The American Journal of Medicine

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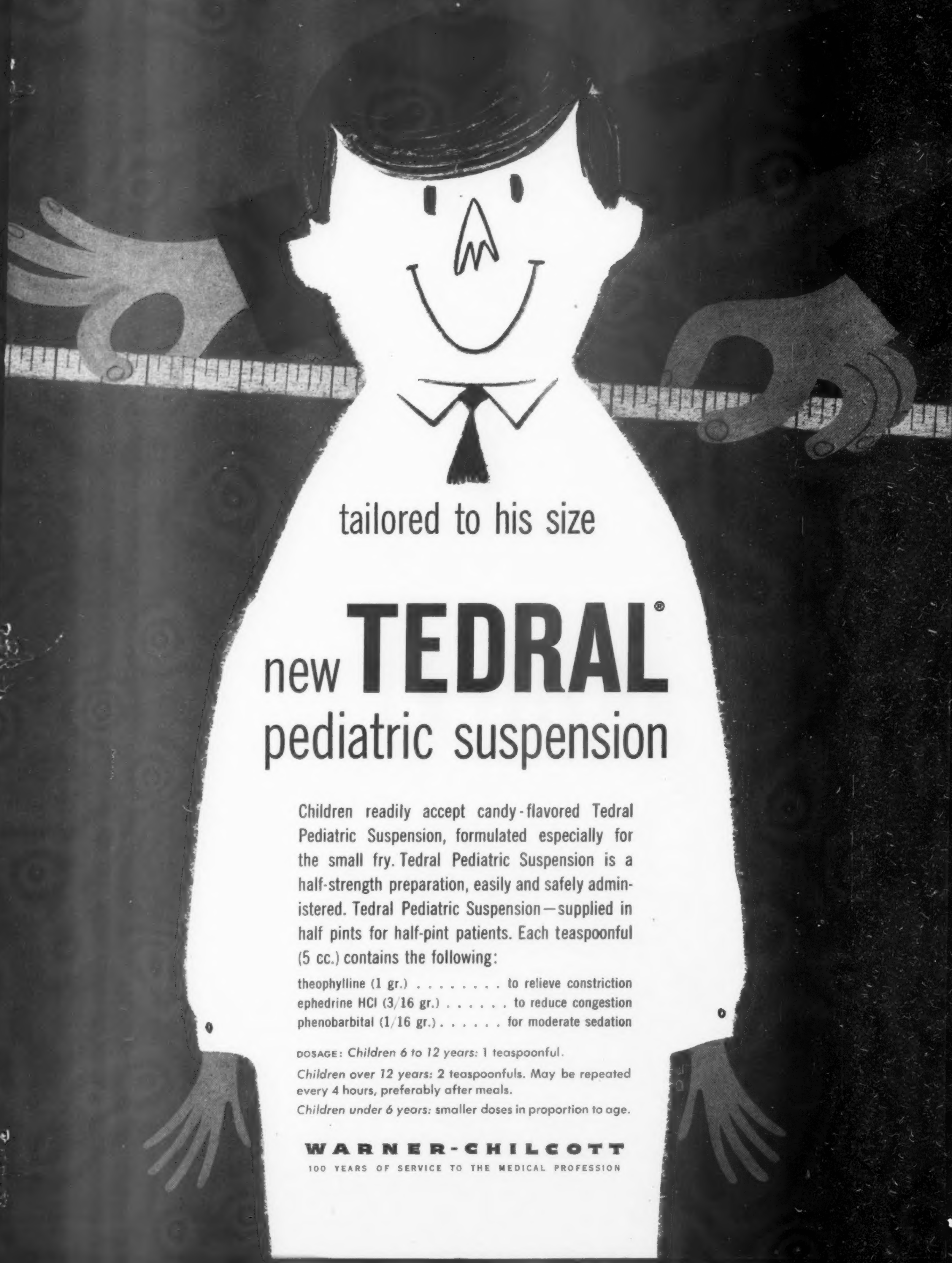
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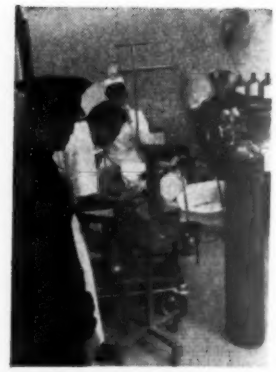

The American Journal of Medicine

Vol. XXIII OCTOBER, 1957 No. 4

CONTENTS

Contents continued on page 5

CONTENTS continued–October 1957

VOLUME TWENTY-THREE NUMBER FOUR

therapy revolves upon recognition of the water and electrolyte imbalance, and recovery hinges upon proper management the importance of awareness and insight needs no emphasis. All this is clearly brought out in the present study, which includes a lucid discussion of "neurogenic hypernatremia" and related phenomena, and common pitfalls in management.

There has been surprisingly little study of the polyuria, with excessive loss of water and electrolytes, which is apt to occur after release of mechanical obstruction of the urinary tract in elderly patients, certainly a common enough clinical event. This analysis of the problem, based on a study of four cases, is therefore welcome indeed. Using standard clearance technics, and the prevailing assumptions regarding the sites and mechanisms of renal conservation of salt and water, it is concluded that the polyuria is essentially due to osmotic diuresis reflecting faulty tubular reabsorption of sodium and chloride, for the most part in the proximal convolution. The delicate problems of management are touched upon.

The introduction of Kolff's disposable artificial kidney has simplified the clinical use of dialysis sufficiently to make it feasible for much wider application than hitherto. What is not yet clear is its clinical usefulness and limitations, hence this informative report of Dr. Kolff's experience in 1956 with ninety dialyses in fifty-two patients is particularly timely. It is apparent that the procedure has severe limitations, yet in some cases of both acute and chronic uremia can accomplish as much as or more than could reasonably be expected, and when all else fails. There are serious inherent hazards but this report indicates that these can be controlled. One may anticipate more extensive and earlier use of this form of management in uremia.

It has already been made clear that more precise examination of infected urine than is ordinarily made is necessary for establishing the diagnosis of pyelonephritis. In the present study correlations were made particularly between the presence of "granular motility" or "glitter" cells and of pale-staining leukocytes with the presence or absence of pyelonephritis as established by renal biopsy. Several interesting observations are recorded which help to clarify the significance of the occurrence of these several cells in the urine sediment. The best correlation with pyelonephritis was found to be with the presence of pale-staining leukocytes. Plausible explanations for this correlation are given.

Contents continued on page 7

CONTENTS continued–October 1957

VOLUME TWENTY-THREE NUMBER FOUR

Review

Contents continued on page 9

CONTENTS continued–October 1957

VOLUME TWENTY-THREE NUMBER FOUR

Advertising Index on Page 105

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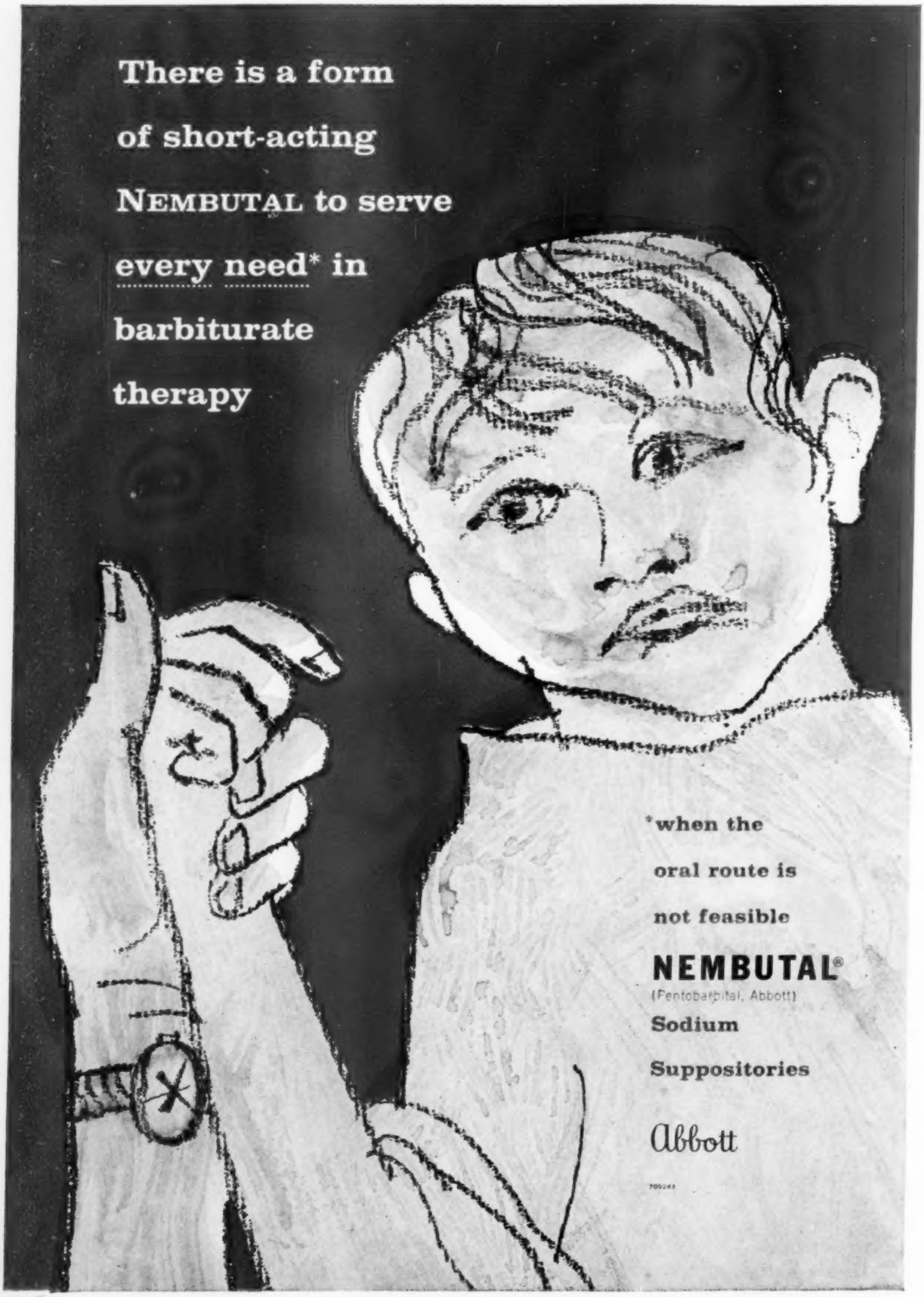
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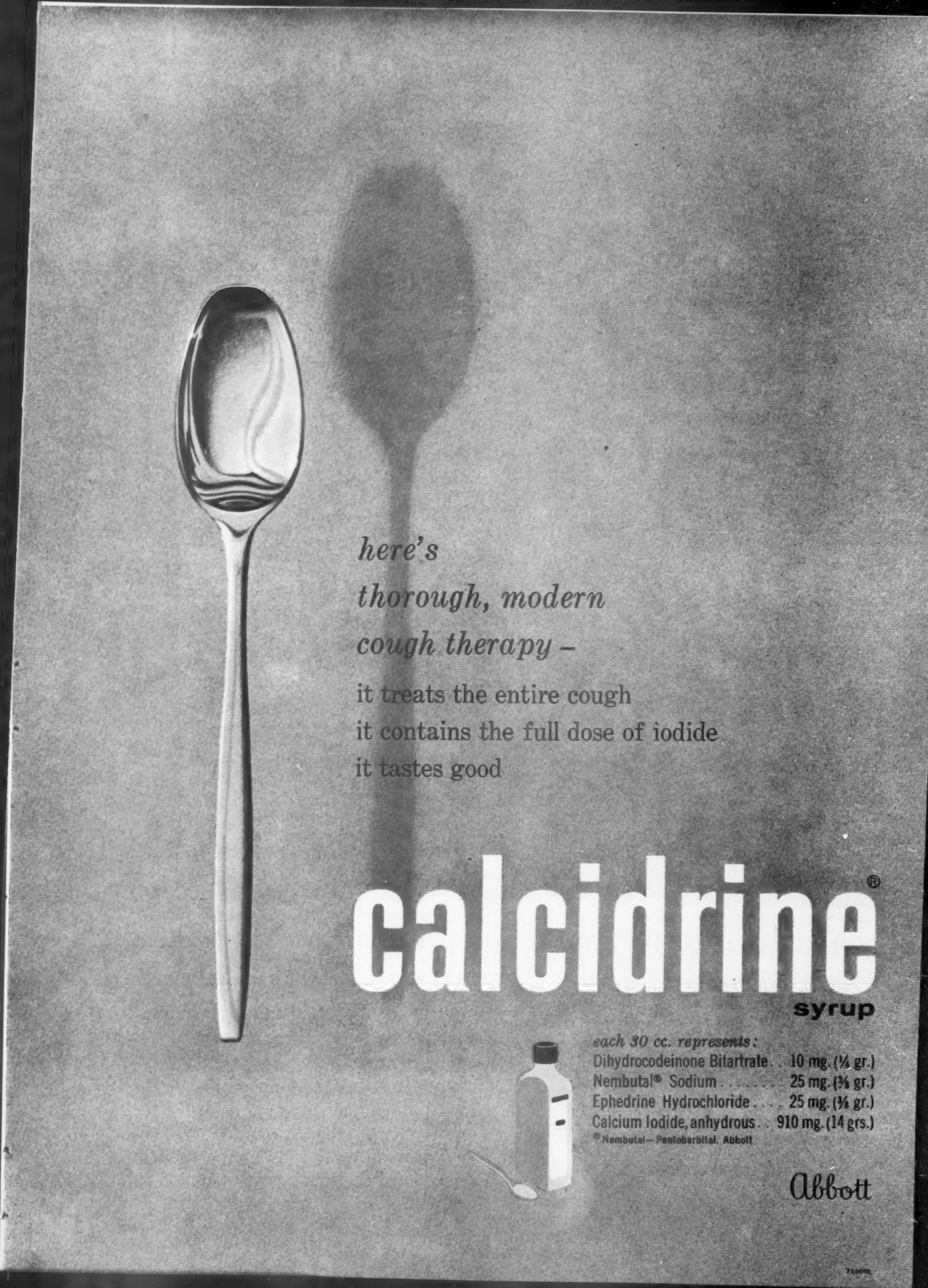
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Diagnosis	No. of Patients	Response				Side Effects
		Excellent	Good	Fair	Negative	
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Urticaria and angioneurotic edema	3	1	1	1		Dizzy (1)
Allergic dermatitis	2		1	1		Slight Drowsiness (2)
Bronchial asthma	1		1			
Pruritus	1		1			
Total	37	15	13	7	2	Drowsiness (5) Dizzy (1) 16.2%

From the preliminary **Dimetane Extentabs** studies of three investigators. Further clinical investigations will be reported as completed.

. . . a distinct advance for these reasons:

POLYMAGMA is the result of significant new findings in antidiarrheal research. Providing powerful individual and collective actions, the POLYMAGMA components include CLAYSORB—a newly discovered adsorbent that is five times as active as centuries-old kaolin. POLYMAGMA contains two complementary antibiotics with proved specificity against many strains of intestinal bacteria, as well as demonstrated synergistic effect. POLYMAGMA is a distinct improvement in antidiarrheal agents. It is distinguished for:

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(the opposite of a tranquilizer)

psychomotor activity (Marsilid stimulates physical and mental activity, appetite and weight gain without objective joint changes).

Q. What is the dosage of Marsilid?

A. The daily dose of Marsilid should not exceed 150 mg (50 mg t.i.d.). In patients who are not hospitalized, the dosage should be reduced after the first 8 weeks to an average of 50 mg daily or less, for Marsilid is a cumulative drug. Like all potent drugs, Marsilid requires careful individual dosage adjustment.

Q. What are the potential side effects of Marsilid?

A. Side effects due to Marsilid are reversible upon reduction of dosage or cessation of therapy. It may cause constipation, hyperreflexia, paresthesias, dizziness, postural hypotension, sweating, dryness of mouth, delay in starting micturition, and impotence.

Q. When is Marsilid contraindicated?

A. Marsilid is contraindicated in overactive, overstimulated or agitated patients. Marsilid therapy should be discontinued two days before the use of ether anesthesia. It should not be given together with cocaine or meperidine. In patients with impaired kidney function, Marsilid should be used cautiously to prevent accumulation. Marsilid is not recommended in epileptic patients.

Q. How is Marsilid supplied?

A. Marsilid is supplied in scored 50-mg, 25-mg and 10-mg tablets.

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COMPARATIVE COMPOSITIONS OF FOOD FATS AND OILS

Fat	Fatty Acids as Percentage of Total Acids: Saturated Ave.	Saturated Range	Oleic Ave.	Oleic Range	Linoleic Ave.	Linoleic Range	Linolenic Ave.	Linolenic Range	Arachidonic Ave.	Iodine Value Average	Iodine Value Range
Butter	—	46-48	—	—	4.0	—	1.2	—	0.2	—	26-42
Coconut oil	—	75-88	—	5-8	—	1.0-2.5	—	—	—	—	7-10
Corn oil	13	11-15	—	23-40	56	46-66	—	0.0-0.6	—	126	113-131
Cottonseed oil	26	21-30	27	22-36	47	34-57	—	—	—	105	90-117
Lard	43	—	46	—	10	15.6	0.5	—	0.5 (2.1)	—	53-77
Linseed oil	—	6-12	—	13-31	—	10-27	—	30-64	—	—	170-204
Margarine	23	15-23	62	59-77	5.8	5-11	—	0.1-0.9	0	81	74-85
Olive oil	—	8-16	—	53-86	—	4-20	—	—	—	—	80-88
Peanut oil	17	14-22	54	44-65	29	20-37	—	—	—	98	90-102
Shortening	25	17-45	62	43-79	5	3-12	—	0.2-0.6	0-0.5	78	59-80
Soybean oil	15	11-18	25	18-58	55	28-62	5.1	0.3-10	—	130	100-143
Tallow (beef)	53	—	42	—	4	5.3	0.5	—	0.5	—	40-48

Iodine numbers are an accepted measure of the degree of unsaturation of vegetable oils.

# of UNsaturated Fatty Acid

Physicians are quite aware of the rapidly growing appreciation of the role of dietary lipids in health and disease. Accumulating metabolic studies throughout the world indicate that serum cholesterol levels may be influenced more by the *kind* than by the *amount* of the dietary fat.

Unsaturated fats tend to depress serum cholesterol levels in many patients, whereas saturated fats may have the opposite effect. Medical references on this subject, as well as other findings concerning unsaturated fatty acids in nutrition, may be found in the book, "Vegetable Oils in Nutrition."

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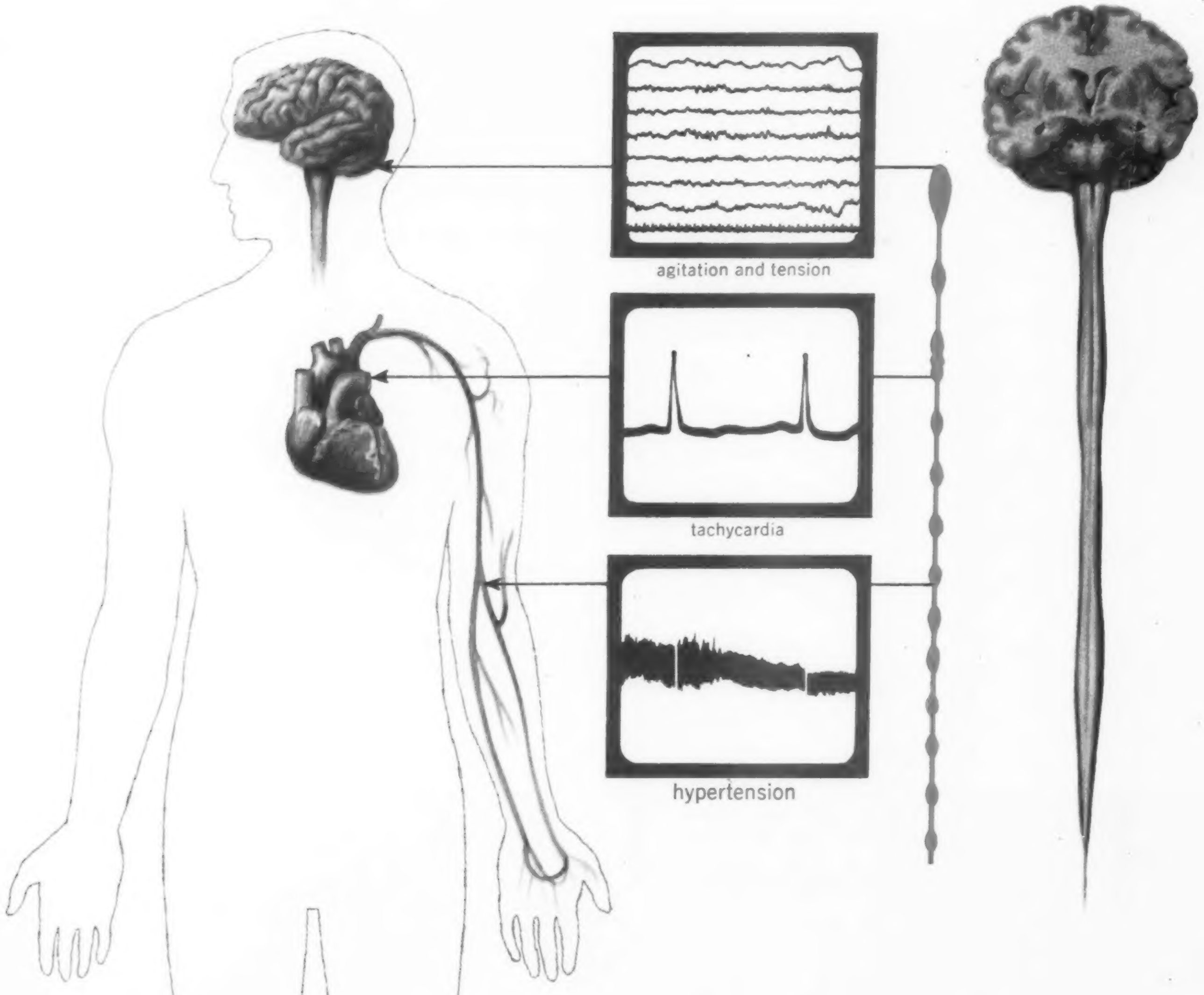
control through sympathetic regulation*



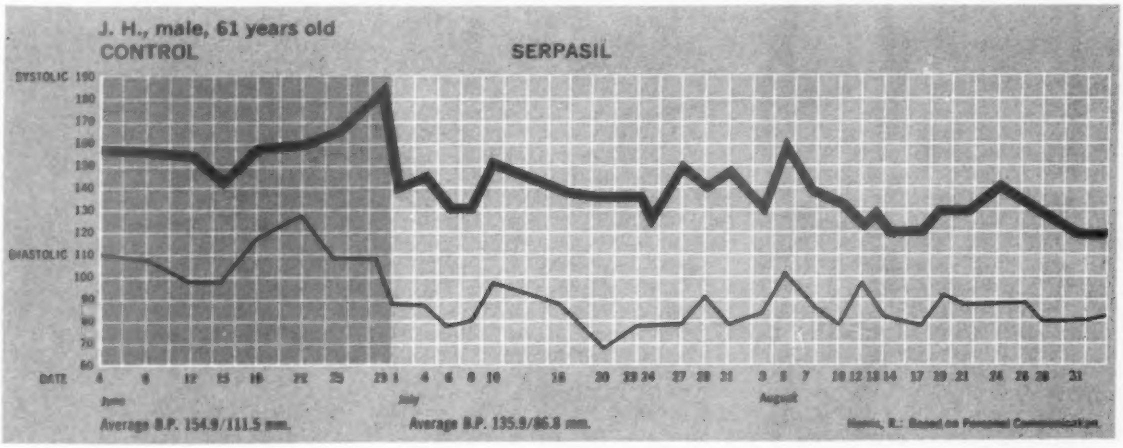
***** *When stress disturbs autonomic balance—by eliciting increased activity of the sympathetic nervous system—hypertension, tachycardia, agitation and many other symptoms you see in everyday practice may result. On the following pages you will see how Serpasil, through its unique ability to regulate sympathetic function, controls these symptoms...*

through sympathetic regulation

...Serpasil® controls high blood pressure

Stress situations produce stimuli which pass through the sympathetic nerves, constricting blood vessels and increasing heart rate. Hyperactivity of the sympathetic nervous system may elevate blood pressure; if prolonged, this may produce frank hypertension. By blocking the flow of excessive stimuli to the sympathetic nervous system, Serpasil guards against stress-induced vasoconstriction, brings blood pressure down slowly and safely.

Effect of 9 weeks of Serpasil therapy on blood pressure of patient with essential hypertension



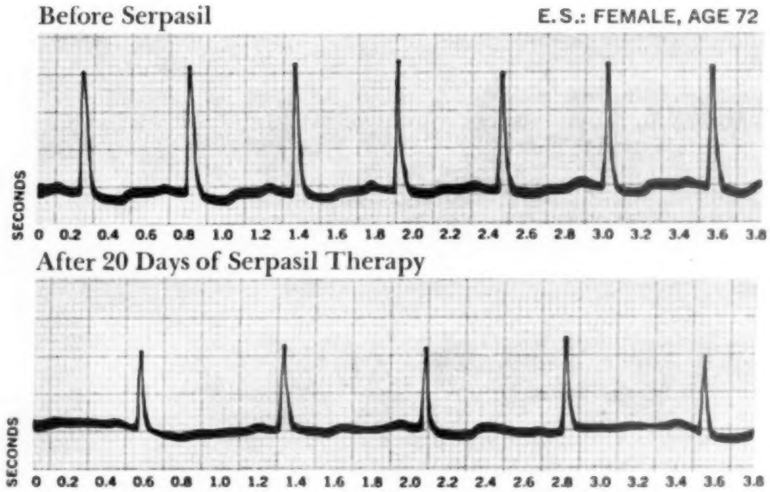
In mild to moderate hypertension, "Serpasil alone is effective in about 70 percent of cases… and is free of virtually any serious side effects."[1]

In severe hypertension, where organic as well as functional changes are implicated, Serpasil is valuable as a ***primer.*** By adjusting the patient to the physiologic setting of lower pressure, Serpasil smooths the way for more potent antihypertensives.

In all grades of hypertension, Serpasil may be used as a ***background agent.*** By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

through sympathetic regulation

Serpasil controls tachycardia



This ECG study demonstrated the heart-slowing effect of Serpasil in an elderly female. Before Serpasil the heart rate was 110 beats per minute. After 20 days of Serpasil (0.5 mg. b.i.d.), heart rate had fallen to 80 per minute.

Harris, R.: Based on Personal Communication.

When stressful situations continue, unresolved, attendant activation of the sympathetic nervous system may unduly stimulate cardio-accelerator fibers, producing tachycardia.

Serpasil allays stress-induced tachycardia through suppression of sympathetic activity. Cardio-accelerator impulses are inhibited and the normal braking action of the vagus allowed to predominate. As a result, cardiac efficiency is enhanced.

Serpasil has been "found useful in relieving the tachycardia and emotional symptoms associated with cardiac arrhythmias, thyrotoxicosis, neurocirculatory asthenia, and even coronary heart disease."[2]

1. Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M.A. *51*:417 (Dec.) 1955. 2. Halprin, H.: J. M. Soc. New Jersey *52*:616 (Dec.) 1955. 3. Kuntz, A.: *The Autonomic Nervous System,* Lea & Febiger, Philadelphia, 1953, p. 458.

low back pain

begins to yield in hours

"... is an orally effective and safe antispasmodic drug. Results are prompt, and gratifying to the patient. The number of office visits ... is reduced significantly. The dosage schedule is simple ... side actions are minimal ..." "No toxic side actions were noted."

Finch, J. W.: Orphenadrine (Disipal) in Skeletal Muscle Disorders. To be published.

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In Parkinsonism

Highly selective action ... energizing against weakness, fatigue, adynamia and akinesia ... potent against sialorrhea, diaphoresis, oculogyria and blepharospasm ... lessens rigidity and tremor ... mildly euphoriant ... safe ... even in glaucoma.

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Brand of Orphenadrine HCl

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superior tetracycline pharmacodynamic action without monilial reaction

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SUMYCIN PLUS MYCOSTATIN

SUMYCIN produces higher initial tetracycline blood levels . . . more immediate tetracycline transport to infection sites . . . notable freedom from side effects.

SUPPLY	Tetracycline phosphate complex equiv. to tetracycline HCl (mg.)	Mycostatin (units)	Packaging
Capsules (per capsule)	250	250,000	Bottles of 16 and 100
Half-Strength Capsules (per capsule)	125	125,000	Bottles of 16 and 100
Suspension (per 5 cc.)	125	125,000	2 oz. bottles
Pediatric Drops (per cc.—20 drops)	100	100,000	10 cc. bottles

Minimum adult dose: 250 mg. of tetracycline q.i.d.

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Rapid relief from inflammatory neuritis—which reduces the cost of this painful disability by permitting patients to resume work quickly—is described by Smith[1,2] and Lehrer et al.[3] By starting PROTAMIDE in the first week of symptoms, 96% of 313 patients recovered with only one to four injections, shortening the duration of disability from weeks to just a few days.[3]

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1. Smith, R. T.: M. Clin. North America, March 1957. 2. Smith, R. T.: New York Med. 5:16, 1952.
3. Lehrer, H.W. et al.: Northwest Med. 75:1249, 1955.


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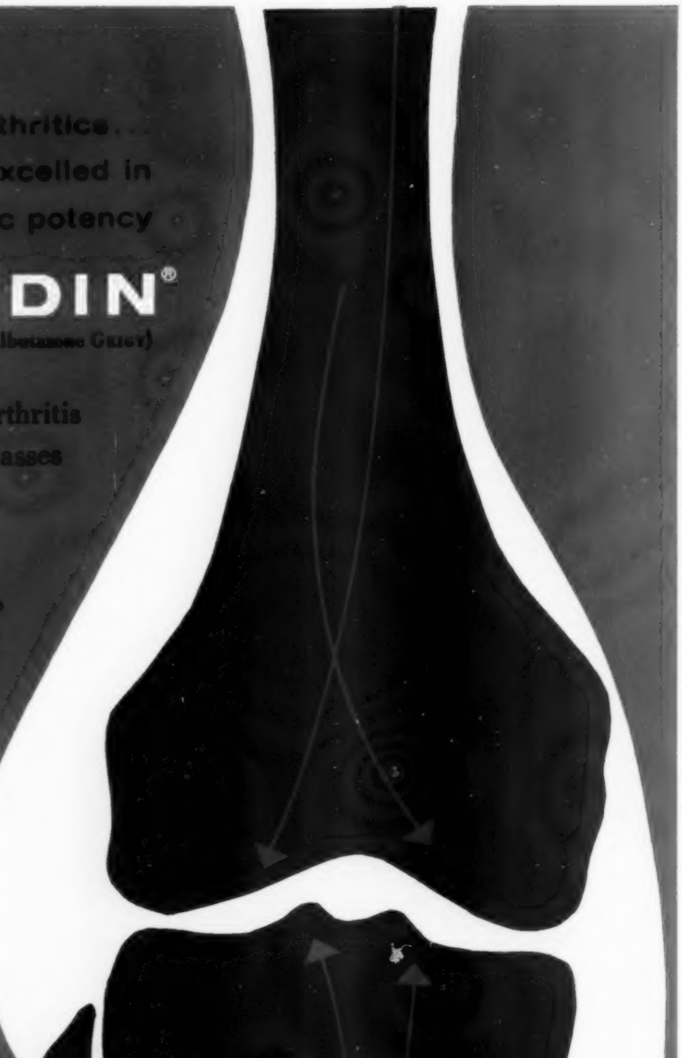
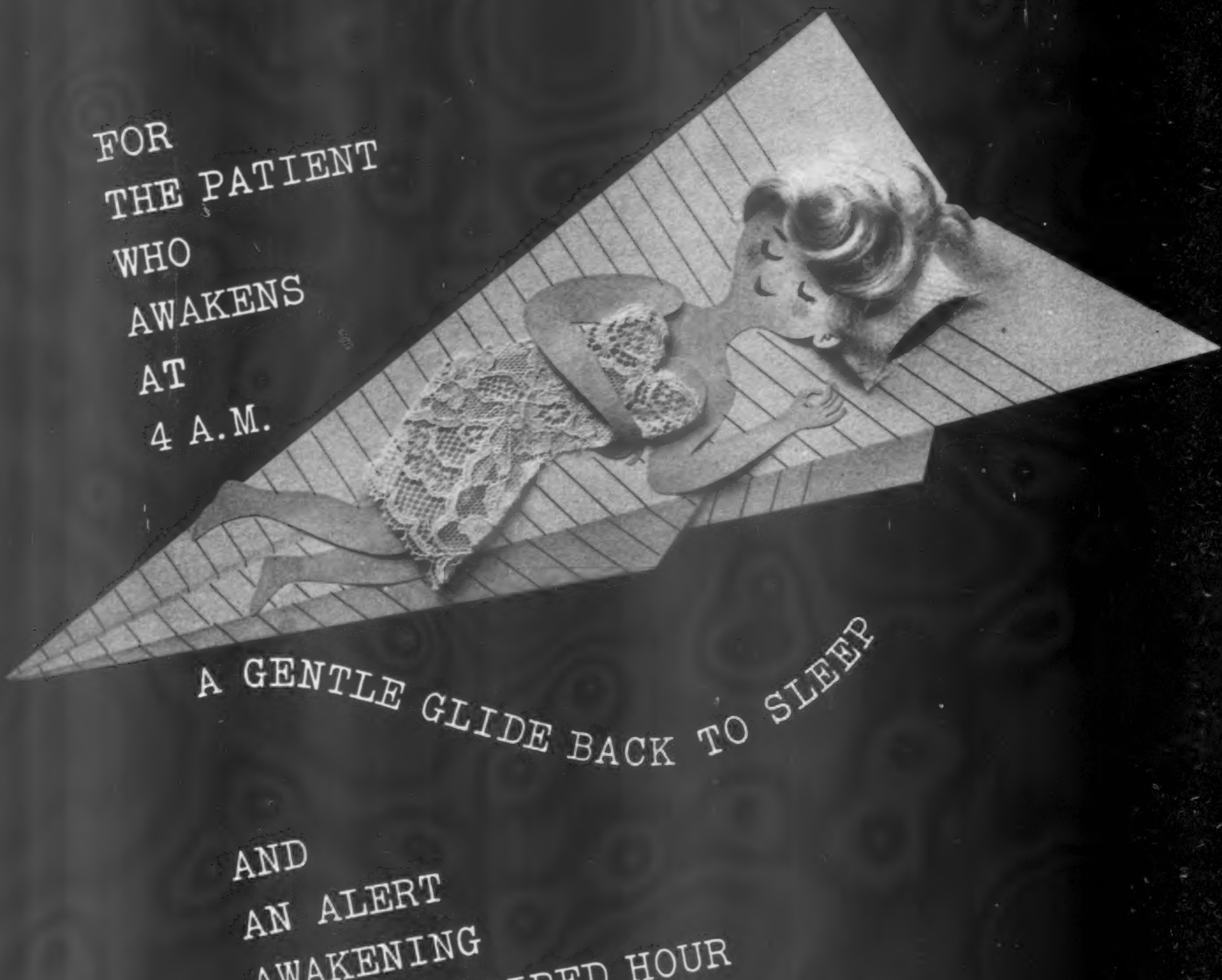


FOR
THE PATIENT
WHO
AWAKENS
AT
4 A.M.



A GENTLE GLIDE BACK TO SLEEP

AND
AN ALERT
AWAKENING
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- At bedtime or for pre-dawn insomnia
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  a ringing telephone or alarm clock
  easily rouses the patient
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- Broad safety margin
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  Noludar is advantageous when it is
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DOSAGE:

two 200 mg tablets gently but firmly
put the confirmed insomniac to sleep.
one 200 mg tablet lulls the geriatric
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The work of many investigators has now culminated in the discovery of Erythropoietin (the erythropoietic hormone).[1,2,3,4] They have confirmed that the newly discovered hormone controls the rate of red blood cell production, and that the rate of R B C formation controls the rate of absorption[5] and utilization of iron.

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Finally, it has been discovered that, acting through physiologic channels, therapeutic cobalt . . . increases red cell production by enhancing the formation of erythropoietin.[6] This provides for the first time the key to the treatment of anemia.

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Cordially yours,
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1. Linman, J. W., and Bethell, F. H.: Blood 11:310, 1956. 2. a) Erslev, A. J.: Humoral regulation of red cell production. Blood 8:349, 1953. b) Erslev, A. J., and Lavietes, P. H.: Observation on the nature of the erythropoietic serum factor. Blood 9:1055, 1954. 3. a) Gordon, A. S.; Piliero, S. J.; Kleinberg, W., and Freedman, H. H.: A plasma extract with erythropoietic activity. Proc. Soc. Exper. Biol. & Med. 86:255, 1954. b) Gordon, A.; Piliero, S.; Tanenbaum, M., and Siegel, C.: Erythropoietic action of a plasma filtrate in hypophysectomized rats. Proc. Soc. Exper. Biol. & Med. 89:246, 1955. 4. a) Fried, W.; Plzak, L. F.; Jacobson, L. O., and Goldwasser, E.: Proc. Soc. Exper. Biol. & Med. 92:203, 1956. b) Plzak, L., et al.: J. Lab. Clin. Med. 46:671, 1955. 5. Bothwell, T. H.; Pribella, W. V., and Hurtado, A.: Intro. by C. A. Finch, 6th Congress, Int. Soc. of Hematology, Boston, Sept. 1, 1956. 6. Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science 125:1085 (May 31) 1957.

NEW RONCOVITE MF
(MODIFIED FORMULA)

ENHANCES ERYTHROPOIETIN FORMATION

TO RAPIDLY CORRECT ANEMIA WITH LOW IRON DOSAGE.

Each green enteric-coated tablet contains:
Cobalt chloride (Cobalt as Co 3.7 mg.) .... 15 mg.
Ferrous sulphate, exsiccated .... 100 mg.

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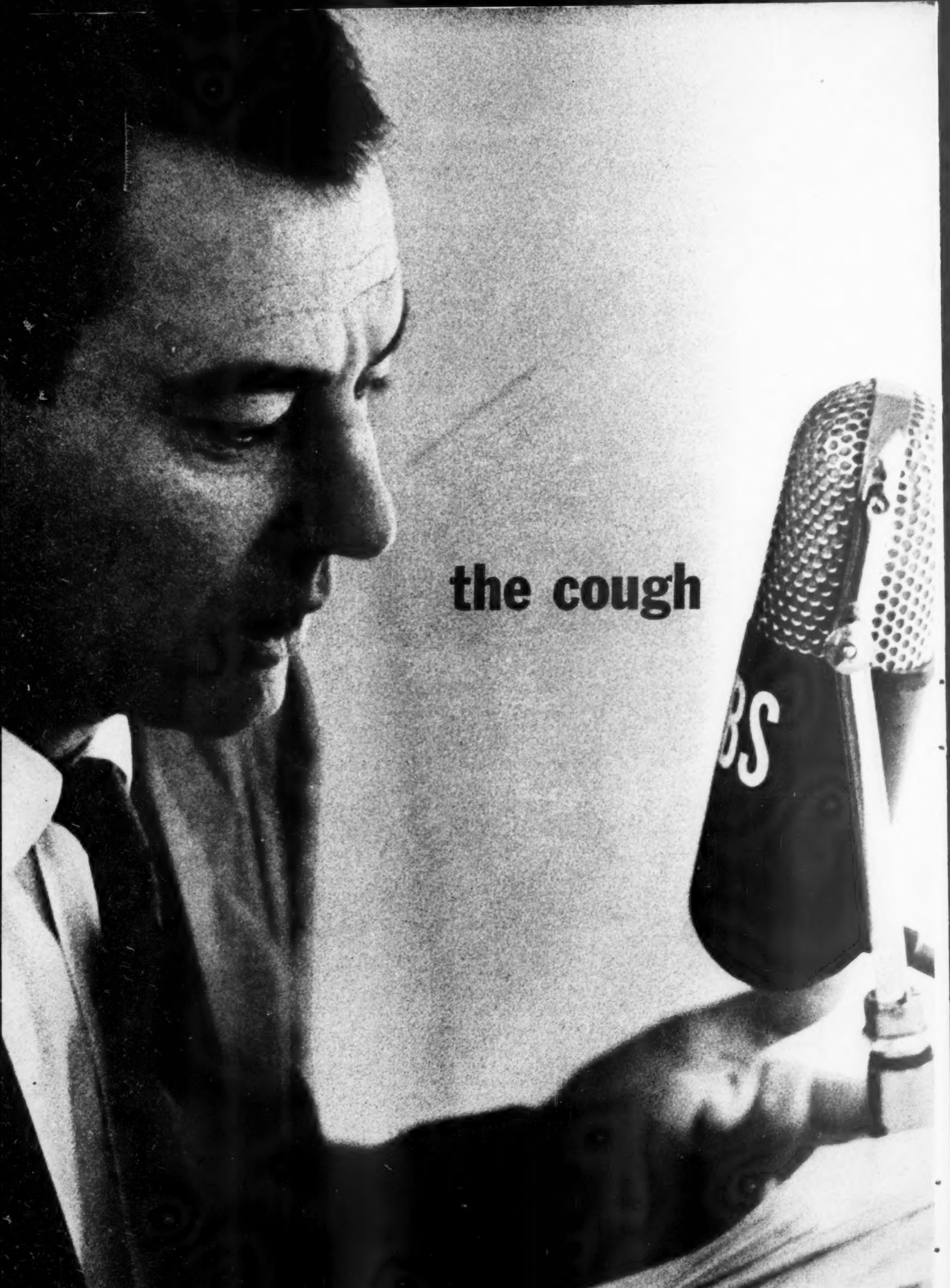
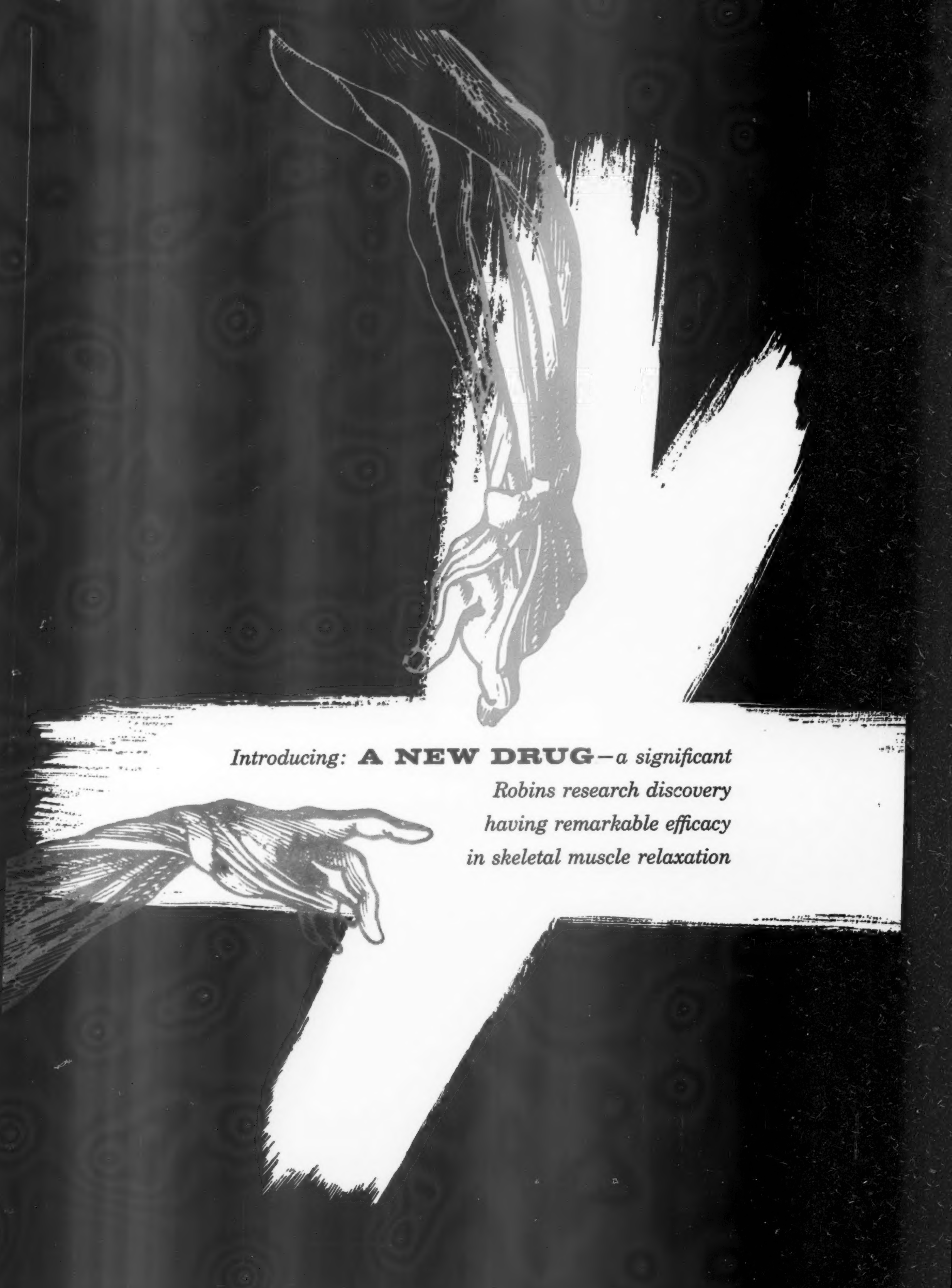

the cough
BS


Introducing: **A NEW DRUG**—*a significant*
Robins research discovery
having remarkable efficacy
in skeletal muscle relaxation

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Highly specific action

ROBAXIN is highly specific in its action on the internuncial neurons of the spinal cord – with inherently sustained repression of multisynaptic reflexes, but with no demonstrable effect on monosynaptic reflexes. It thus is useful in the control of skeletal muscle spasm, tremor and other manifestations of hyperactivity, as well as the pain incident to spasm, without impairing strength or normal neuromuscular function.

Beneficial in 94.4% of cases tested

When tested in 72 patients with acute back pain involving muscle spasm, ROBAXIN induced marked relief in 59, moderate relief in 6, and slight relief in 3 – or an over-all beneficial effect in 94.4%.[1,3,4,6,7] No side effects occurred in 64 of the patients, and only slight side effects in 8. In studies of 129 patients, moderate or negligible side effects occurred in only 6.2%.[1,2,3,4,6,7]

CLINICAL RESULTS WITH ROBAXIN IN ACUTE BACK PAIN[1,3,4,6,7]

Disease entity	No. of Cases	Duration of Treatment	Dose per day (divided)	Response				Side Effects
				Marked	Mod.	Slight	Neg.	
Acute back pain due to								
(a) Muscle spasm secondary to sprain	18	2-42 days	3-6 Gm.	17	1	0	0	None, 16; Dizziness, 1; Slight nausea, 1.
(b) Muscle spasm due to trauma	13	1-42 days	2-6 Gm.	8	1	3	1	None, 12; Nervousness, 1.
(c) Muscle spasm due to nerve irritation	5	4-240 days	2.25-6 Gm	4	1	0	0	None, 5.
(d) Muscle spasm secondary to discogenic disease and postoperative orthopedic procedures	30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25; Dizziness, 1; Lightheadedness, 2; Nausea, 2.*
Miscellaneous (bursitis, torticollis, etc.)	6	3-60 days	4-8 Gm.	6	0	0	0	None, 6.
TOTAL	72			59	6	3	4	

*Relieved on reduction of dose

A PRODUCT OF ROBINS RESEARCH

NOW

a highly specific skeletal muscle relaxant...

Robaxin®

(Methocarbamol Robins)

This new drug–for use in the control of skeletal muscle hyperactivity in many disease states manifesting neuromuscular dysfunction–is available NOW on your prescription at all leading pharmacies. Informational literature is available on request.

Indications:

Acute back pain associated with: (a) muscle spasm secondary to sprain; (b) muscle spasm due to trauma; (c) muscle spasm due to nerve irritation; (d) muscle spasm secondary to discogenic disease and postoperative orthopedic procedures; and (e) miscellaneous conditions such as bursitis, torticollis, and related conditions.

Dosage:

ADULTS: 2 tablets 4 times a day to 3 tablets 6 times a day.

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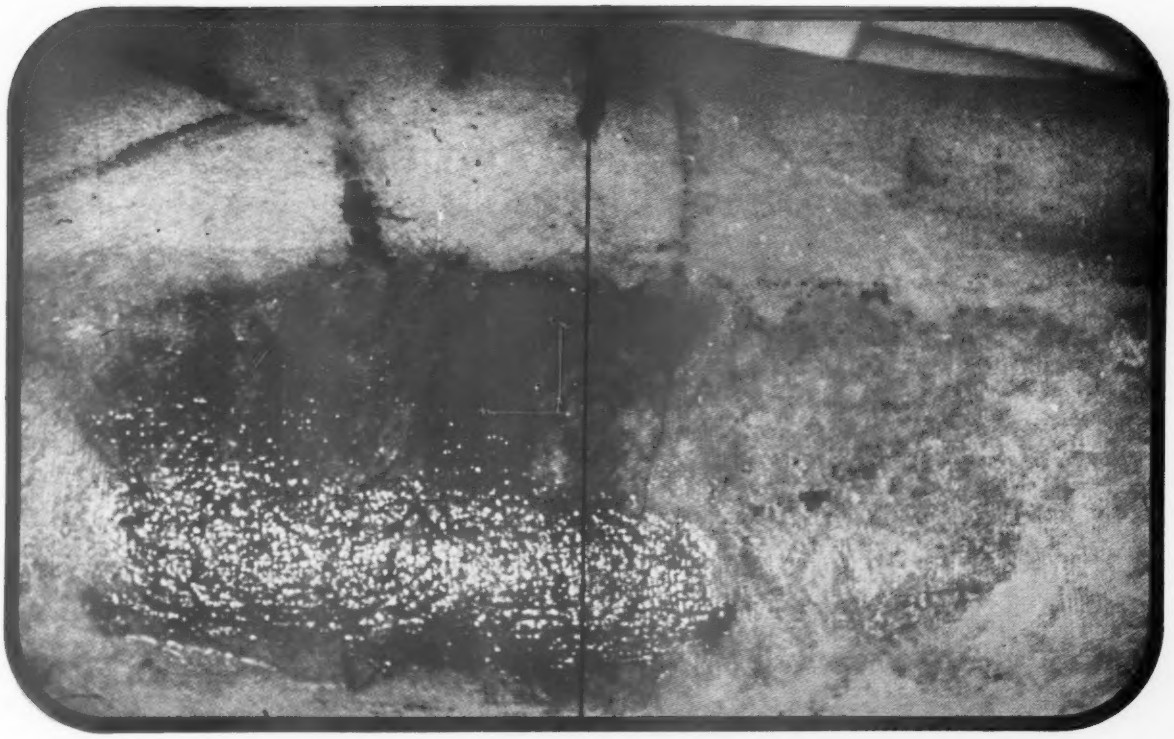

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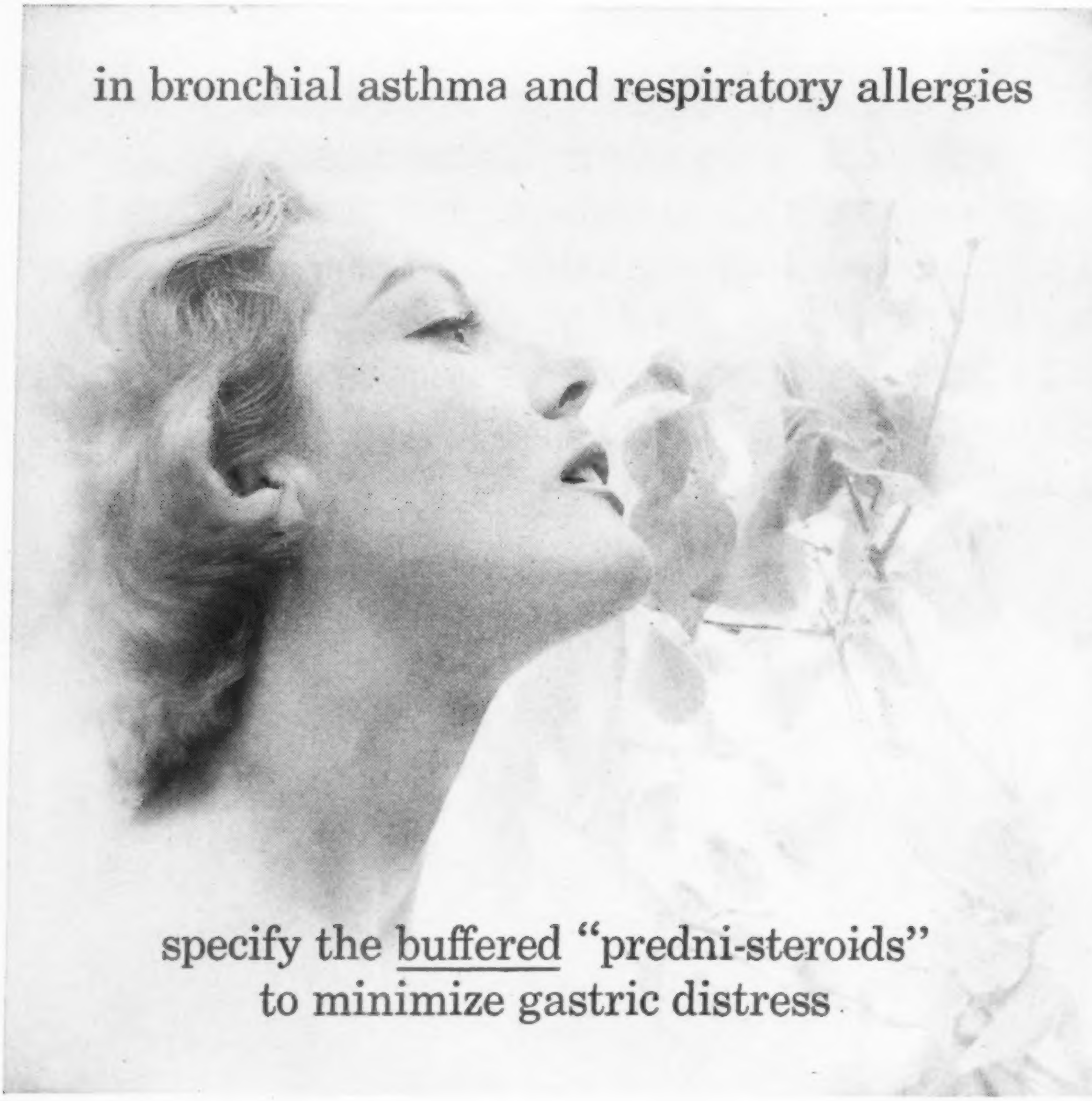

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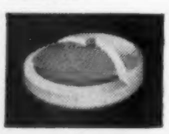

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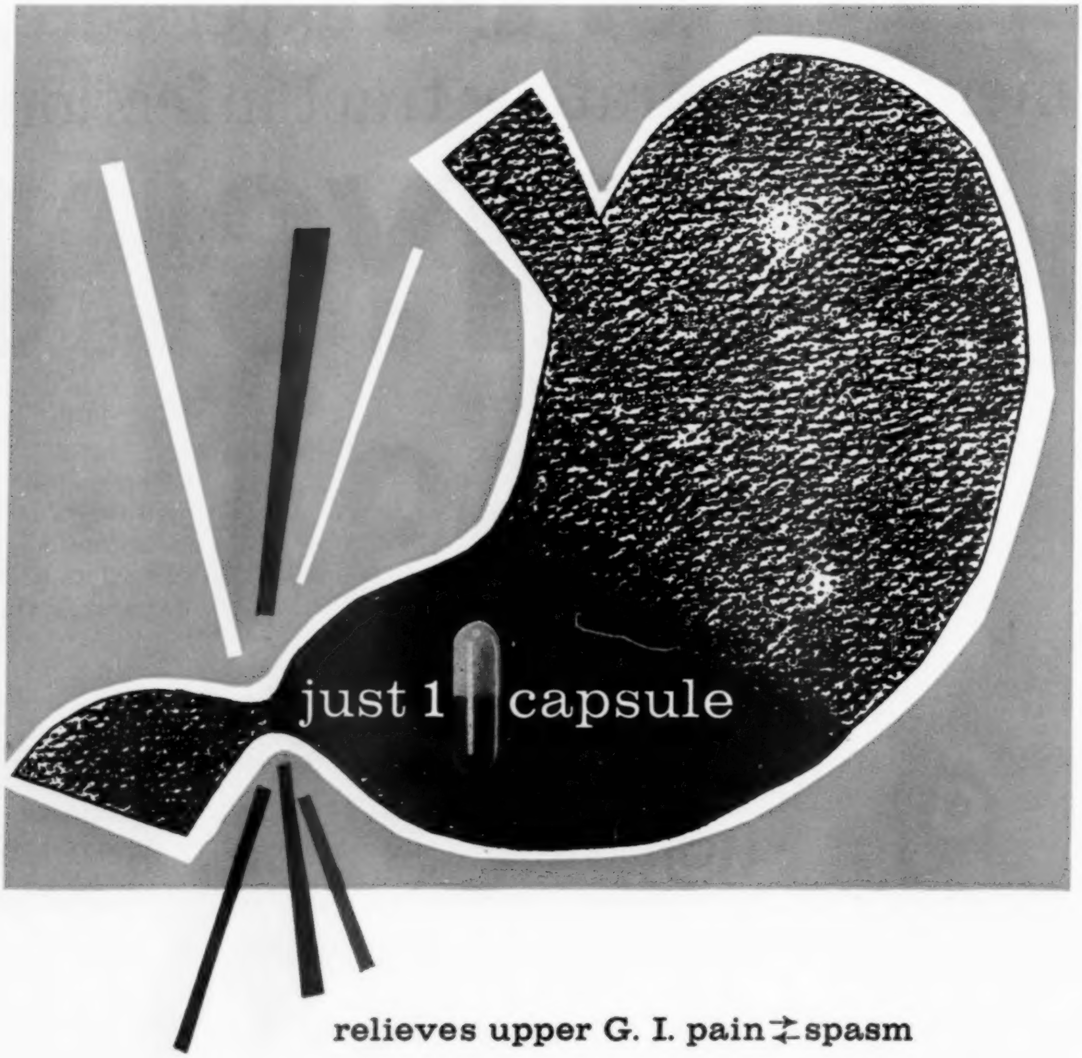

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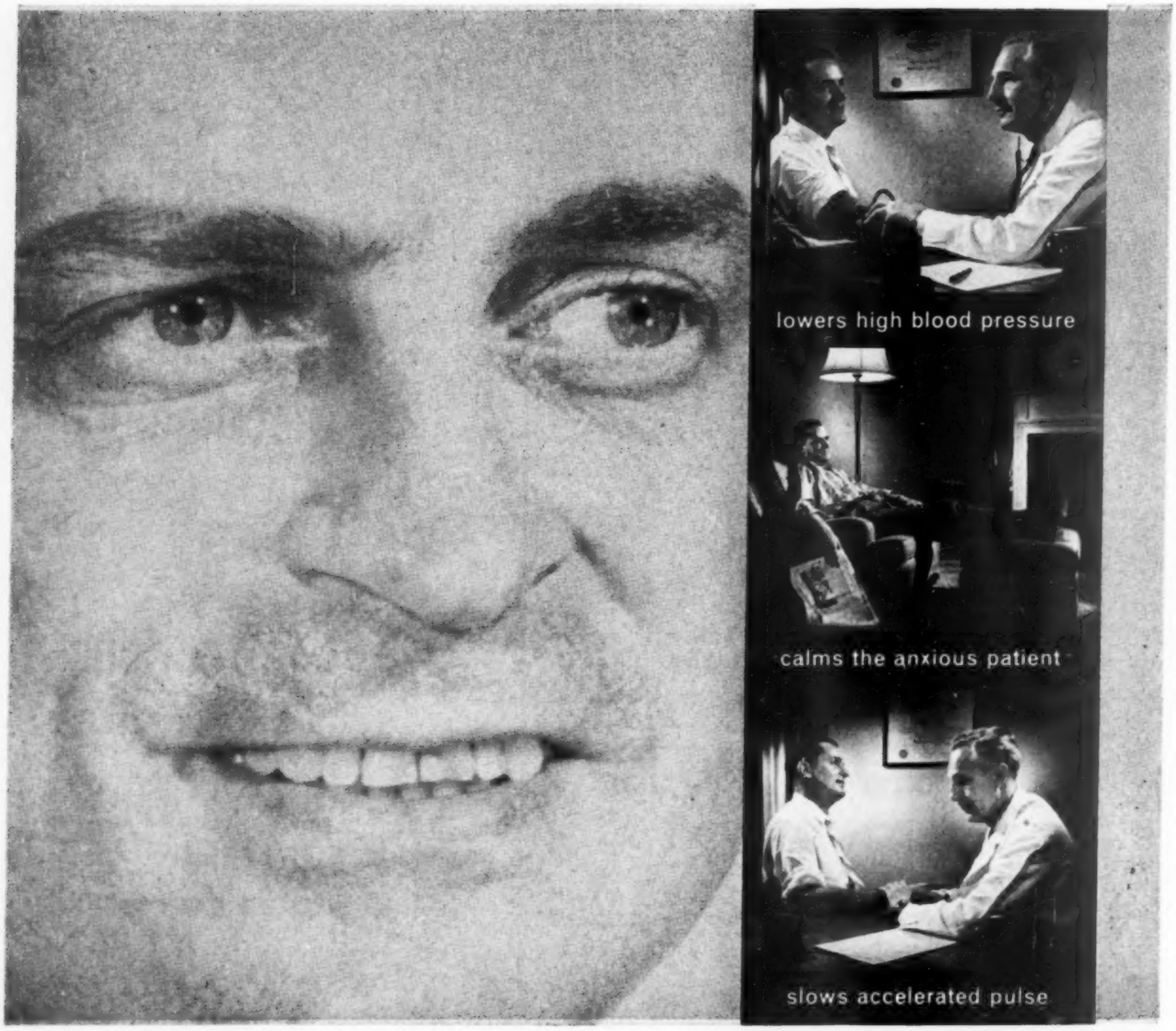

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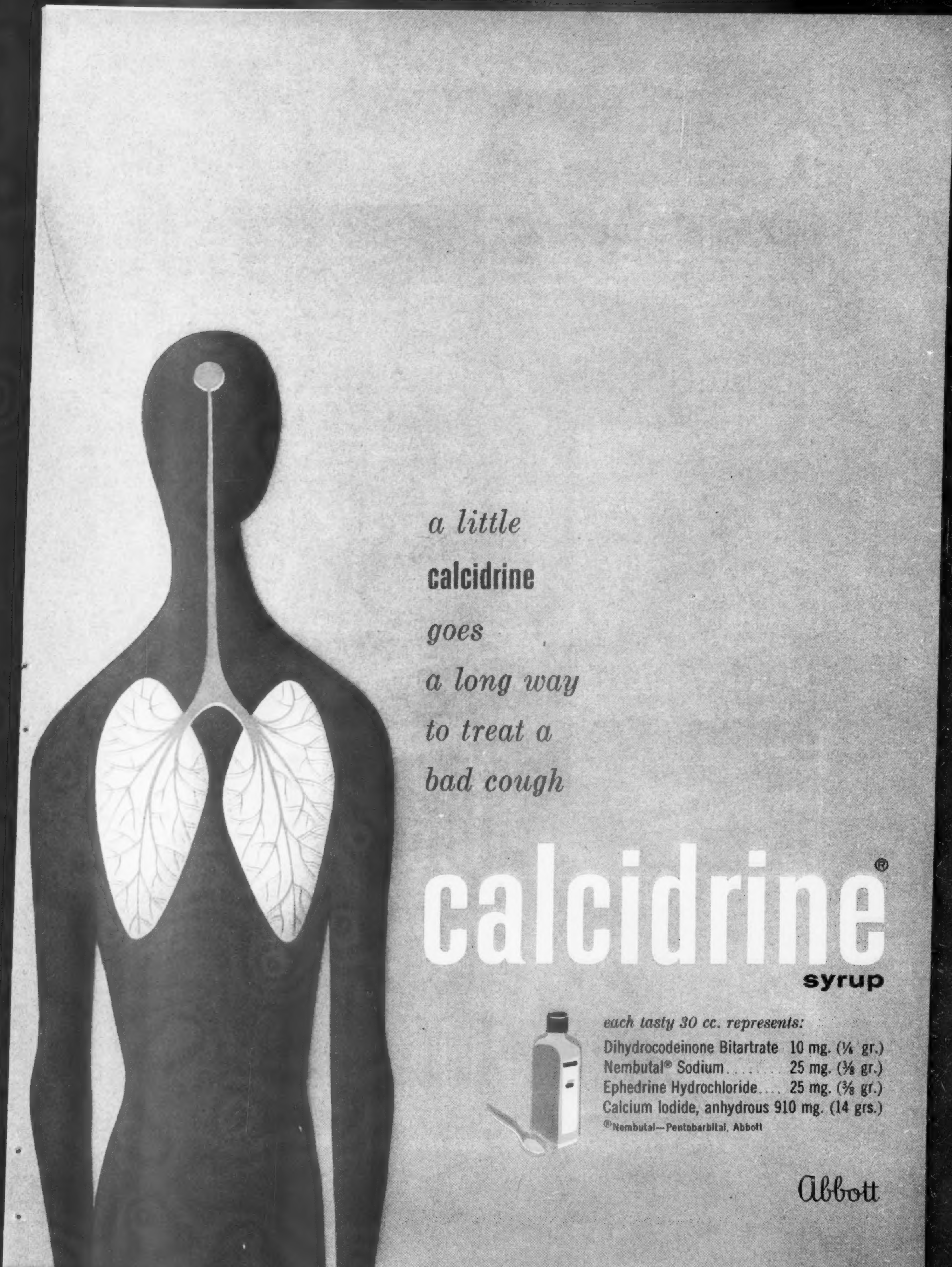
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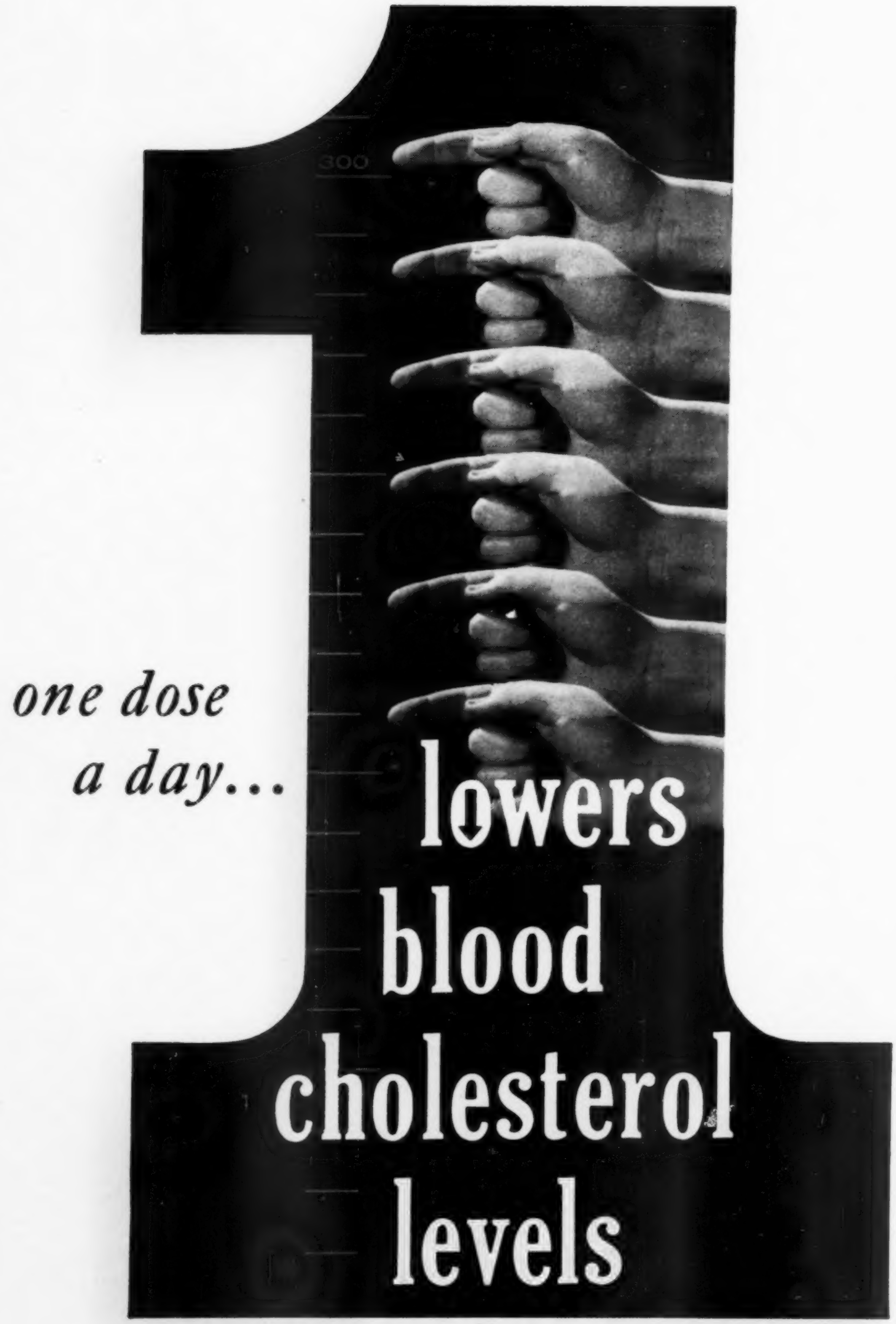
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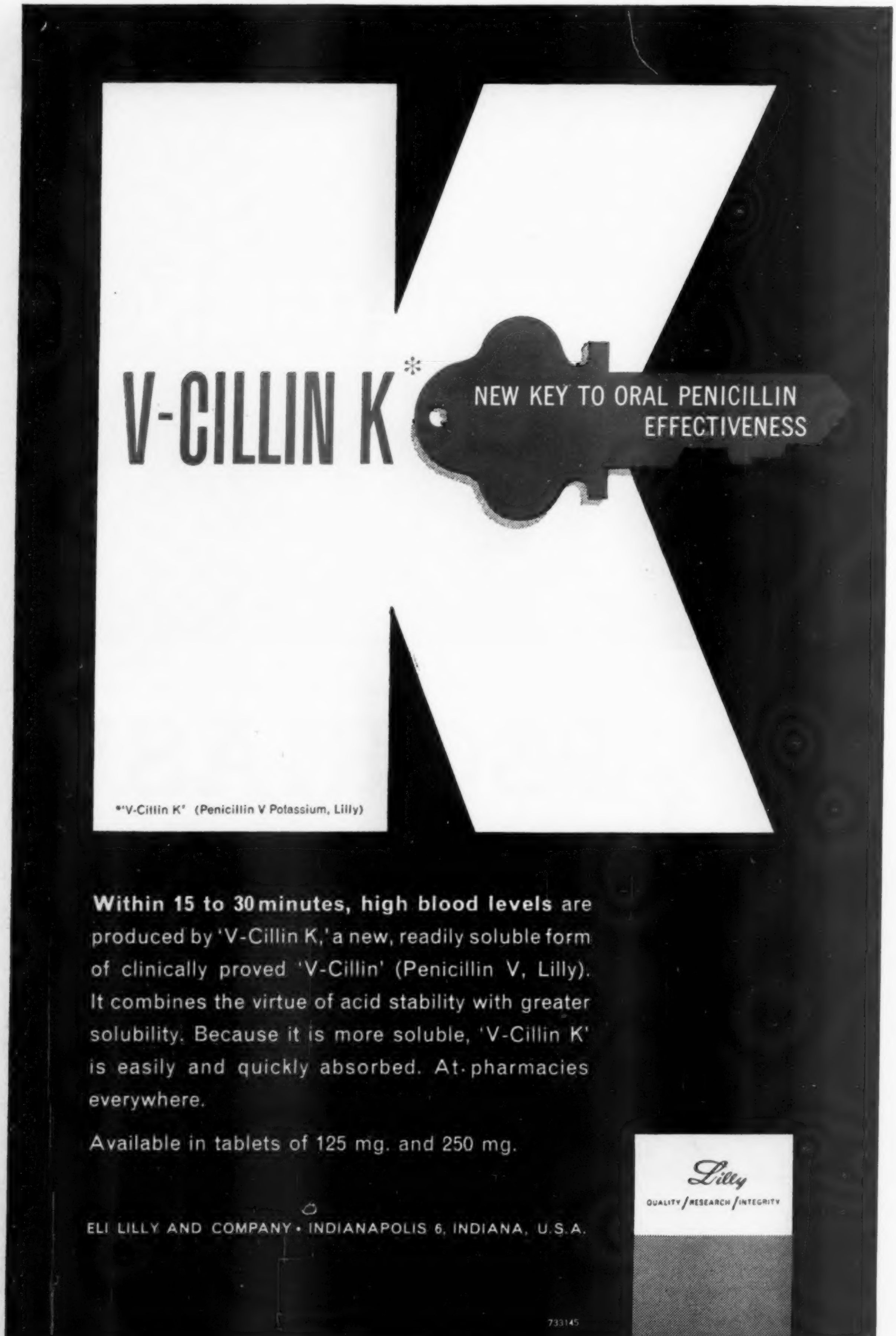
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Vol. XXIII OCTOBER, 1957 No. 4

Editorial

Cyclical Edema

Cyclical episodes of edema in the absence of demonstrable cardiac, renal or hepatic disease constitute a well recognized clinical entity which is confined almost entirely to adult female patients [*1*]. The maximal gain in weight is observed most frequently during the immediate premenstrual period but may appear in midcycle or following cessation of menstruation. The syndrome has been observed in postmenopausal patients as well.

Obesity increases the predisposition to cyclical edema. The retention of sodium and water is usually associated with increased nervousness and irritability and in the more severe cases with headache and nausea. Patients with the more serious and persistent form of the syndrome often exhibit deep-seated psychologic disturbances. These abnormalities may be overlooked or minimized by the physician during the initial examination if his attention is focused on uncovering serious organic disease. The presence of a significant psychologic factor in so many of these patients and the apparent interruption of the edema cycles which has been observed in some patients with psychotherapy alone [*2*] emphasize the effect of this influence on the disabling complaints associated with the syndrome and perhaps even on the genesis of the pathophysiologic changes.

Recently it has been demonstrated that patients with cyclical edema may exhibit elevated levels of aldosterone in the urine [*1,3*]. One might also predict that in some patients high levels of antidiuretic hormone (ADH) will also be found. What do these hormonal changes imply? Why is this syndrome rarely seen in men who are equally well supplied with endogenous aldosterone and ADH? Through what mechanisms may psychologic disturbances precipitate excessive fluid retention? In discussing these questions one must first consider certain well established physiologic principles.

Cycles. Cyclical changes in important biologic constituents of the body are known to occur in both men and women. The magnitude of the changes is far greater in women and obviously more complex. Not only do the cyclical changes involve alterations in hormonal secretions and mineral metabolism, but more recently the importance of cyclical changes in blood and alveolar carbon dioxide levels has been reemphasized. Striking changes in carbon dioxide levels appear regularly in relation to the onset of menstruation and pregnancy. Of great interest is the recent observation [*4*] that the administration of progesterone results in alteration in the level of alveolar carbon dioxide in both male and

[1] Thorn, G. W., Renold, A. E., Froesch, E. R. and Crabbe, J. Pathophysiology of edema. *Helvet. med. Acta,* 23: 3, 1956.

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female subjects [4,5]. Similar changes have not been observed with other male or female sex hormones or with 17-hydroxysteroids. It is not necessary to point out the direct effect which changes in carbon dioxide tension may exert on the activity of critical regulating centers in the brain. The early establishment of a fundamental cyclical rhythm alternately involving the retention and release of sodium and water provides the female patient with a deep-seated, well integrated mechanism which may in times of stress be subject to pathologic variations. The association, normally, of fluid retention with ovulation, menstruation and pregnancy further identifies this particular physiologic phenomenon with climactic experiences.

Female Sex Hormones. It is well known that estrogens and progesterone are capable of inducing sodium retention [6] and that an appreciable number of normal women, particularly if obese, retain increased quantities of sodium, chloride and water during the immediate premenstrual period [7]. Such retention is often associated with increased nervousness, irritability and restlessness. To date it has not been possible to correlate excessive fluid retention in these patients with greater than normal estrogen or progesterone (pregnandial) excretion. The magnitude of the salt and water retention is diminished but not abolished by hysterectomy. Studies on a patient following bilateral ovariectomy failed to disclose significant cycles of sodium and chloride retention [7].

The absence of cyclical edema in female patients prior to the menarche and the relative rarity of the syndrome in postmenopausal women suggest the importance of the cyclical changes in female sex hormone secretion as a conditioning mechanism through which excessive retention of salt and water may occur. There is no evidence at present, however, to indicate that a quantitative change in female sex hormone secretion is the critical factor in precipitating the development of the syndrome.

[5] Robin, E. D., Tyler, J. N., Travis, D. M., Crump, C. H. and Thorn, G. W. The effect of progesterone on the respiration of normal males and patients with chronic hypercapnia. To be published.

[6] Thorn, G. W. and Engel, L. L. The effect of sex hormones on the renal excretion of electrolytes. *J. Exper. Med.*, 68: 299–312, 1938.

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Aldosterone. The demonstration of elevated urinary aldosterone levels in female patients with cyclical edema immediately raises the question of whether or not the development of the syndrome is dependent upon increased aldosterone secretion. Primary hyperaldosteronism, as exemplified by the Conn syndrome, is characterized by hypokalemia, hypochloremia, a metabolic alkalosis, a normal sodium concentration in the urine and no edema. Secondary hyperaldosteronism is characterized by edema and a low urinary sodium concentration. Thus it would appear that female patients exhibiting cyclical episodes of edema with increased aldosterone values probably represent a form of secondary hyperaldosteronism. This may have been initiated during the development of the syndrome and is most certainly enhancedby procedures designed to mitigate it, i. e., dietary sodium restriction and diuretics such as diamox® and mercurial administration. To evaluate the role of elevated urinary aldosterone values (and presumably increased secretion of aldosterone) it has been suggested that amphenone, or similarly acting substances, be administered in an effort to determine the effectiveness of reducing aldosterone levels on urinary sodium excretion [1,8]. It has been shown that certain patients with edema due to congestive failure or hepatic cirrhosis fail to respond to amphenone with a brisk sodium diuresis whereas other patients may respond rather promptly. Thus, although one could not, from studies of this type, deduce the factors which lead to increased aldosterone in patients with cyclical edema, one could, at least, obtain evidence of the pathogenetic significance of the hyperaldosteronism in the syndrome at the time amphenone is administered. There would appear to be no doubt but that in certain patients the magnitude of the cyclical edema is enhanced by increased aldosterone secretion. There is no evidence at present to indicate that the hyperaldosteronism is primary.

Antidiuretic Hormone (ADH). It is difficult to assess the role of altered ADH secretion in the development of the syndrome. A slow, steady gain in weight associated with sodium retention and low urinary sodium concentration suggests that salt-retaining factors are primarily responsi-

[8] Renold, A. E., Crabbe, J., Hernando-Avendano, L., Nelson, D. H., Ross, E. J., Emerson, K., Jr. and Thorn, G. W. Inhibition of aldosterone secretion by amphenone in man. *New England J. Med.*, 16–21, 1957.

ble for the edema and that water retention is secondary. Weight gain with a normal urinary sodium concentration, or very rapid gain in weight over a period of twenty-four to thirty-six hours, with oliguria, suggests increased ADH activity. Such a case of cyclical edema in which oliguria and the symptoms of water intoxication became manifest with great suddenness *after* the cessation of menstruation has been encountered by the author. To date, difficulties in assaying the antidiuretic hormone have limited investigation of disturbances of the mechanism in patients with cyclical edema.

Capillary Permeability. Alteration in capillary permeability would provide a simple explanation for cyclical retention of fluid. Attempts have been made to establish the presence of alteration in capillary permeability in patients with cyclical edema but conclusive changes have not been demonstrated. It is recognized, of course, that a subtle change in permeability probably nondetectable by present methods, operating over a period of hours or days could account for the accumulation of an appreciable quantity of fluid. It is interesting to note that a number of patients with cyclical edema have experienced a severe streptococcus infection early in life, suggesting the possibility of injury or increased sensitization of capillary epithelium to subsequent stress.

Organic Disease. The presence of renal disease or heart disease may, of course, markedly enhance the quantity of fluid retained during the premenstrual period [*9*]. This response can, at times, become so marked as to suggest a serious change in the underlying organic process. Obviously, factors such as hypoproteinuria, congestive heart failure, hepatic cirrhosis and renal disease may be expected to enhance the quantitative aspects of cyclical edema. The physician is well advised to keep this fact in mind, particularly in female patients who are scheduled to undergo elective cardiac surgery.

Other Considerations. Patients sometimes complain of "distention" or increased girth without necessarily exhibiting an appreciable increase in weight. In most patients this does not appear to be due to distention of the bowel but may be explained by alterations in intra-abdominal pressure as a result of changes in skeletal muscle tone. Increased food intake, salt craving and polydypsia all enhance the total effect brought about by physiologic mechanisms which induce salt and water retention. Behavioral changes including increased irritability and restlessness are common accompaniments of the syndrome. Finally, it should be noted that the symptoms expressed by a patient may be entirely out of proportion to the physical changes involved—suggesting the importance of phantasies concerning the body image in the symptomatology of the syndrome.

Conclusion. Important cyclical changes in salt and water balance become firmly established at an early date in the reproductive life of the female. Alterations in the secretion of female sex hormones, aldosterone and ADH provide important mechanisms through which this normal phenomenon may be enhanced. Alterations in capillary permeability and in fluid and salt intake provide additional means by which the total change may be effected. Obesity and certain organic diseases enhance the magnitude of the response. The close neuroregulatory control involved in all of these physiologic mechanisms, coupled with the demonstration of significant underlying psychologic factors in many patients, suggest that the cyclical episodes of edema may be explained as an exaggeration of a normal phenomenon by emotional stress. This concept gains support from the fact that symptomatology is so often out of proportion to the quantity of salt and water retained, and that psychotherapeutic measures alone apparently influence the cycles in some cases. Certainly the preoccupation of the physician with metabolic minutia to the exclusion of psychologic and emotional factors is almost certain to lead to failure in treatment. To emphasize the importance of psychologic factors in the genesis and clinical manifestations of this syndrome, the term "psychlical edema" has been suggested. An appreciation of the importance of psychologic as well as physiologic factors in these cases may help to minimize the use of diuretics and hormonal agents and prevent unnecessary surgery such as ovariectomy and adrenalectomy!

George W. Thorn, M.D.
Peter Bent Brigham Hospital,
Boston 15, Massachusetts.

[9] Thorn, G. W. Physiologic considerations in the treatment of nephritis. *New England J. Med.*, 229: 33–48, 1943. (The Shattuck Lecture, May 25, 1943.)

Clinical Studies

Acute Nephritis Unrelated to Group A Hemolytic Streptococcus Infection*

Report of Ten Cases

RICHARD C. BATES, M.D., ROBERT B. JENNINGS, M.D. *and* DAVID P. EARLE, M.D.
Lansing, Michigan *Chicago, Illinois*

CONSIDERABLE clinical, bacteriologic and immunologic evidence indicates that the great majority of instances of acute glomerulonephritis follow group A hemolytic streptococcal infections [*1–8*]. Longcope [*7*], for instance, found evidence of preceding group A hemolytic streptococcal infections in 72 per cent of thirty-six patients with acute glomerulonephritis (type A). Likewise, Lyttle and his colleagues [*8*], using serial measurements of the serum antistreptolysin titer, demonstrated recent streptococcal infection in 94 per cent of 116 cases of acute nephritis.

Rammelkamp and his co-workers [*9–11*] have shown that several strains of hemolytic streptococci, notably type 12 and to a lesser extent types 4 and 25, are most commonly associated with acute glomerulonephritis. Rammelkamp's observations have been confirmed [*12–15*] and recently an epidemic of acute glomerulonephritis associated with infections due to a previously unrecognized type of group A hemolytic streptococci has been described [*16*].

Despite the obvious frequency of the association of group A hemolytic streptococcal infections with acute glomerulonephritis, infections due to other organisms have been incriminated. Thus, acute diffuse glomerulonephritis undoubtedly may occur as a complication of subacute bacterial endocarditis due to Streptococcus viridans and perhaps other organisms [*17,18*], and rarely may follow pneumococcic lobar pneumonia [*19*]. Recently several instances of acute glomerulonephritis have been described in association with trichinosis [*20*]. However, evidence of streptococcal infection was presented in the protocols of two of three patients who had renal damage.

Although a number of other infections such as gastroenteritis, ulcerative colitis [*21*], typhoid fever, typhus and scrub typhus [*22*], infectious mononucleosis [*23*], vaccinia [*24,25*], measles, mumps and influenza have been said from time to time to be occasional precursors of acute glomerulonephritis, no evidence was presented that ruled out the possibility of incidental or complicating hemolytic streptococcal infections, or that acute glomerulonephritis was the cause of proteinuria and hematuria observed in some patients.

In 1926 Baehr [*26*] reported the case histories of fourteen young adults who suffered from what he described as "a benign and curable form of acute hemorrhagic nephritis." Gross hematuria was the outstanding clinical feature, occurring intermittently in some patients and continuously in others. Pharyngitis preceded the onset of hematuria by a few days and always by less than eight days in the intermittent form. The continuous form was associated with "chronic tonsillitis." Baehr stated that no specific evidence of hemolytic streptococci was found but no significant data were presented on this point. Edema, hypertension and impairment of renal function did not occur. The disease was not progressive in any patient. A few similar cases were described by Scheidemordil in 1915 [*27*]

* From the Departments of Medicine, Great Lakes Naval Hospital, Great Lakes, Illinois and the Medical School, Northwestern University; and the Department of Pathology, The Medical School, Northwestern University, Chicago, Illinois. This work was supported in part by grants from the Otho S. A. Sprague Foundation and the U. S. Public Health Service, National Institutes of Health, Bethesda, Maryland (H-1815, H-1890). Views expressed are those of the authors and do not necessarily reflect the opinion of the Navy Department.

TABLE I
GREAT LAKES NEPHRITIS GROUP
ASSOCIATED INFECTION

Patient	Age (yr.)	Penicillin Prophylaxis		Character of Infection	Treatment of Infection	Maximum Temperature (°F. oral)	Duration of Fever or Symptoms (days)	White Blood Cells (cu. mm.)	Lymphocytes (%)	Sedimentation Rate (mm./hr.)
		Dose (units)*	Days Before Onset Infection							
Arc.	18	200,000 orally	64 to 12	Pharyngitis	None	98.6	2	6,500	25	6
Bra.	17	600,000 intramuscularly	26	Pharyngitis	Terramycin	103	5	5,400	45	11
Gol.	19	600,000 intramuscularly	21	Pharyngitis, Pneumonitis	None	104	13	9,000	32	..
Jan.	21	None	....	None known	None	98.6	..	11,500	..	10
Kee.	18	600,000 intramuscularly	8	Pharyngitis	Penicillin	102	7	7,700	43	37
Lai.	25	None	....	Pharyngitis	None	100	4	8,300	38	25
Mar.	17	None	....	Pharyngitis	None	103.4	3	5,200	48	31
Nic.	17	600,000 intramuscularly	17	Pharyngitis, Tonsillitis	Terramycin	103	7	7,500	32	3
Smi.	18	None	....	Pharyngitis	Gantrisin	100.8	3	5,000	..	32
Wea.	19	None	....	Pharyngitis, Tonsillitis	Penicillin	103.8	3	......	..	20

* All intramuscular doses-benzathine penicillin.

and by Volhard and Fahr in their book which was published in 1914 [*28*]. Volhard and Fahr believed that such instances represented focal glomerulonephritis. Bell [*29*] and others likewise have described hemorrhagic acute glomerulonephritis of a similar type which appears to have an excellent prognosis and which they believed to be associated with focal damage to glomerular capillary loops but with little or no cellular proliferation. Again, bacteriologic and immunologic evidence bearing on the presence or absence of group A hemolytic streptococcal infections was not available.

Between January 6 and July 26, 1956 ten recruits with clinical findings compatible with acute glomerulonephritis were admitted to the Great Lakes Naval Hospital, Great Lakes, Illinois from the adjoining Recruit Training Camp. Although nine of these patients had pharyngitis, serial measurement of serum antibodies excluded recent group A hemolytic streptococcal infections in all but one patient. Adequate renal biopsy specimens were obtained in nine of the ten patients. The present report describes the clinical, immunologic and pathologic features observed in this small outbreak of nephritis. As will become apparent, some doubt exists as to whether or not two of these patients had acute nephritis of the same type.

For comparison, there is presented a similar but condensed analysis of data obtained from eleven patients with acute glomerulonephritis presumably associated with group A hemolytic streptococcal infections. The latter group was observed by us during the same period of time encompassed by the Great Lakes outbreak. Six of these patients were military personnel who contracted acute glomerulonephritis in various parts of the world and were transferred to the Great Lakes Naval Hospital for further evaluation. The remaining patients were residents of Chicago and were studied in Northwestern University Medical School affiliated hospitals.

General Circumstances of the Great Lakes Naval Station Outbreak. Eight of the patients were admitted to the hospital between January 6 and April 3, 1956, one was admitted in June and one in July. The latter two patients (Jan and Mar in the tables) differed from the rest of the group in several respects which are to be discussed later. They are included in the analysis, however, since their renal disease was discovered under circumstances similar to the others. The patients were all recruits from the adjoining Recruit Training Camp, ranging in age from seventeen to twenty-five years. Because of yearly outbreaks of type 19 streptococcal infections in the training camp, many recruits received penicillin prophylaxis shortly after arrival at the camp. Five patients had been given either oral penicillin or intramuscular benzathine penicillin prophylactically within five weeks of the onset of their disease. Data concerning the penicillin prophylaxis are included in Table I. Throat cultures were made daily by the Naval Medical Research Unit No. 4 on representative samples of recruits during the

period of penicillin prophylaxis. During the period of prophylaxis, group A hemolytic streptococci of virtually all types were absent from the recruit population. No type 12 hemolytic streptococci were found. Unfortunately, none of the patients with acute nephritis was included in the throat culture study group.

Associated Infections. Great Lakes Nephritis Group. One patient (Jan) had no evidence of recent infection but the other nine had pharyngitis. (Table I.) Two had follicular tonsillitis in addition. Patient Gol, who had fever for thirteen days and a cough productive of blood-streaked sputum, exhibited x-ray evidence of a pneumonitis, interpreted by the radiologist as being characteristic of "viral pneumonia." Cold agglutinins did not develop. Eight of nine patients with overt infection had (oral) temperatures that exceeded 100°F. and were febrile for two to thirteen days. White blood cell counts made during the period of pharyngitis ranged from 5,000 to 11,500 per cu. mm. Only two patients had counts in excess of 9,000 per cu. mm. The highest count occurred in the patient without overt infection. Differential white blood cell counts were performed in seven patients. Lymphocytes ranged from 25 to 48 per cent of the total counts. The erythrocyte sedimentation rate (Wintrobe) was 20 mm. or more in the first hour in five of nine patients in whom this test was made near the time of infection. Unfortunately, throat cultures were obtained from only a few of the patients. No pathogens were found. Five patients received antibiotics or sulfonamide drugs for their respiratory infections. Three of ten patients received neither prophylaxis nor treatment for their respiratory infections.

Titers of serum antibodies against hemolytic streptococci were measured in all patients. Antistreptolysin 0 titers (ASO) were measured by the method of Rantz and Randall [*30*], antistreptokinase (ASK) by the method of Christensen [*31*], and antihyaluronidase [AH] by the method of Harris and Harris [*32*]. Variations in antibody titers that did not exceed two tubes were not considered significant. Type-specific antibodies against type 12 hemolytic streptococci were measured by Stollerman's modification [*33*] of the bactericidal method of Todd [*34*]. Type 12 antibodies were selected for study since infections due to this organism are most commonly associated with acute glomerulonephritis. These data are presented in Table II. Adequate serial observations of ASO, ASK and AH serum titers in eight patients revealed no evidence of a recent group A streptococcal infection. The first observations in patient Smi were not obtained until the thirteenth week after his pharyngitis. Thus, an earlier transient increase in antibodies could not be excluded. However, the relatively low antibody titers observed between the thirteenth and twenty-third weeks made a recent group A hemolytic streptococcal infection unlikely. The data obtained in patient Wea were compatible with a recent streptococcal infection, although not conclusive. The behavior of the ASO and ASK titers in this patient are more suggestive of a streptococcal infection some months in the past than at the time of the pharyngitis associated with the gross hematuria.

Only one of the patients (Lai) had antibodies against type 12 hemolytic streptococci. Since these antibodies were demonstrated during the fourth week following pharyngitis and at a time when the ASO, ASK and AH titers were low, this patient's exposure to type 12 hemolytic streptococci presumably occurred some time in the past and was not associated with the present episode.

Clinical Features. Great Lakes Group. The latent period between the onset of pharyngitis and the first sign of acute glomerulonephritis did not exceed five days in any of the nine patients with overt infection. (Table III.) In patients Arc and Kee gross hematuria preceded the first symptoms of pharyngitis by one and by three days, respectively, while hematuria developed within twenty-four hours after the onset of pharyngitis in three others.

The presenting feature of renal disease (Table III) was gross hematuria in seven patients. Routine urinalysis on admission to the dispensary for the pharyngitis revealed a sediment loaded with erythrocytes in one of the other patients, and occasional erythrocytes in the remaining two patients (Jan and Mar). All patients had proteinuria on admission, ranging from a trace in one to 3 plus. Likewise, all patients had casts in the urinary sediment. Red blood cell casts were seen in four. Transient periorbital edema was noted in two patients. Only one patient (Jan) had moderate pitting edema of the pretibial area on admission; this persisted for five days. Hypertension lasting for one or two days occurred in two patients. Azotemia of one week's duration developed in only one patient (Wea), who was the only one

TABLE II
GREAT LAKES NEPHRITIS GROUP
SERUM ANTIBODIES

Patient	Antibody	Weeks After Onset of Infection																							
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Arc.	ASO	(100)			50			50		50															
	ASK				160			320																	
	AH				181			128		128															
	12							Negative																	
Bra.	ASO			50		50			50								50								
	ASK			160		320											160								
	AH			181		45																			
	12											Negative													
Gol.	ASO		200		100		125						125												
	ASK		40				80																		
	AH		32				32																		
	12						Negtive																		
Jan.	ASO					50				50															
	ASK					40		20		40															
	AH																								
	12																Negative								
Kee.	ASO		125	125		200	200		200					200											
	ASK		160	160			160																		
	AH		181	181																					
	12													Negative											
Lai.	ASO			50				50		50						50									
	ASK			80				80																	
	AH			90				45																	
	12			Positive										Positive											
Mar.	ASO		50																						
	ASK		40						80																
	AH																								
	12								Negative																
Nic.	ASO	(100)	(100)	(50)		50	50		50						50										
	ASK					80	80								80										
	AH					128	181																		
	12					Negative	Negative								Negative										
Smi.	ASO													50		50						50			50
	ASK													160		80									
	AH													181											
	12													Negative		Negative									Negative
Wea.	ASO						333		166		166			166			166		166					250	
	ASK						640				320								160						
	AH						90				90														
	12													Negative					Negative						

NOTE: ASO = antistreptolysin titer (units)
ASK = antistreptokinase titer (units)
AH = antihyaluronidase titer (units)
12 = type 12 hemolytic streptococcal antibodies
( ) = Determinations not made in our laboratory

who had any considerable degree of impairment of concentrating ability. Five other patients exhibited slight impairment of concentrating ability. Urea clearance was moderately reduced in one of six patients, while phenolsulfonphthalein excretion was normal in each of three patients studied.

Serial observations of serum complement (Table IV) were made by the technic of Mayer and colleagues [*35*]. Significant reductions were observed in eight of ten patients. One of the exceptions, patient Gol, suffered from a complicating pneumonitis, while the other exception, patient Mar, had a positive C-reactive protein test although no clinical evidence of an inflammatory process could be found. Curiously,

TABLE III
GREAT LAKES NEPHRITIS GROUP
CLINICAL DATA

Patient	Latent Period (days)	Edema	Maximum Blood Pressure (mm. Hg)	Urine: Initial: Protein	Urine: Initial: Red Blood Cells (per high power field)	Urine: Initial: Casts	Urine: Duration (days)*: Protein	Urine: Duration (days)*: Red Blood Cells	Urine: Duration (days)*: Casts	Urine: Final: Protein	Urine: Final: Red Blood Cells (per high power field)	Urine: Final: Casts (per high power field)	Maximum Blood Urea Nitrogen (mg. %)	Minimum 18-hr. Conc.	Minimum Urea Clearance (ml./min.)
Arc	−1	0	138/65	1+	Gross	Cellular	25	25	25	0	0	0	18	1.031	68
Bra	5	0	156/76	1+	Many	Cellular	2	107+	107+	0	0–5	0–2	18	1.027	..
Gol	3	0	110/75	1+	Gross	Granular	38	127+	60	0	Occasional	0	10	1.025	..
Jan	?	2+	160/96	3+	8–10	Hyaline; granular	100+	100+	44	4+	3–5	0	10	1.020	67
Kee	−3	0	120/74	1+	Gross	Cellular	43	124+	124+	0	0–5	Granular	15	1.022	68
Lai	1	0	120/80	2+	Gross	Granular	46	54	46	0	0	0	16	1.032	41
Mar	1	Periorbital	116/64	2+	Occasional	Granular	55+	55+	46	3+	0–3	0	18	1.018	22
Nic	5	0	132/70	Trace	Gross	Cellular	2	149+	90	0	15–20	0	12	1.022	..
Smi	5	Periorbital	116/64	2+	Gross	Granular	45	162+	77	0	20–40	0	14	1.020	52
Wea	1	0	114/76	3+	Gross	Granular	122	157+	122	0	10	0	52	1.011	..

* Still present at last observation on day indicated.

TABLE IV
GREAT LAKES NEPHRITIS GROUP
SERUM COMPLEMENT (UNITS)

Patient	Weeks after Onset: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Arc				26			28		29															
Bra	—		28	32	35			26								25								
Gol		51*		41		42						37							40					
Jan					34		35		23															
Kee		43	39		33	40		45					43											
Lai				34			35		35				30		33									
Mar			37						37															
Nic	—				28	29		25			29			37				35						
Smi													32		26						32			
Wea						38		33		34			35					39					36	50

NOTE: Normal serum complement = 40 to 50 units.
Duration of proteinuria indicated by underlines.
Arrow = present at last observation.

decreased serum complement values persisted in many of the patients after the disappearance of proteinuria.

Paper electrophoretic patterns of the serum proteins were developed by the technic of Durrum [36] in all patients. (Table v.) Significant reduction in the percentage of albumin in the first serums studied was noted in three patients and slight reductions in two others. Gamma globulin exceeded 20 per cent of the

total proteins in seven of ten patients. The maximum value of 29.7 per cent occurred in patient Gol who had pneumonitis. Unfortunately, the first paper electrophoresis pattern was obtained four or more weeks after the onset of acute nephritis in five patients. One patient (Mar)

TABLE V
GREAT LAKES NEPHRITIS GROUP
INITIAL SERUM PROTEINS
(PER CENT DISTRIBUTION—PAPER ELECTROPHORESIS)

Patient	Days After Onset	Protein Fractions (% of total protein)				
		Albumium	Globulins			
			α_1	α_2	β	γ
Arc.......	24	48.6	4.8	8.2	16.5	21.9
Bra.......	10	51.2	4.1	8.5	12.6	23.6
Gol.......	8	34.0	5.0	17.8	13.5	29.7
Jan.......	44	35.2	6.5	16.7	22.1	19.5
Kee.......	10	39.4	5.9	8.9	22.9	22.9
Lai.......	28	45.9	5.2	9.9	18.6	20.4
Mar......	18	44.6	4.9	18.1	16.2	16.2
Nic.......	30	50.4	5.3	9.3	10.6	24.4
Smi.......	77	53.8	2.9	11.9	14.3	17.1
Wea......	38	50.5	2.8	12.1	12.6	22.0

had a total serum cholesterol value of 378 mg. per cent. Nevertheless, only patient Jan could be considered to have had the nephrotic syndrome. Approximately one month after onset in this patient, who exhibited 3 to 4 plus proteinuria throughout observation, 2 plus pitting edema of the lower legs redeveloped. His serum albumin decreased to 3 gm. per cent but his serum cholesterol level remained normal.

The period of observation of the patients ranged from fifty-five to 162 days after the apparent onset of the nephritis. At the end of the observation period proteinuria, as revealed by weekly urinalysis, had disappeared in eight patients. (Table III.) Proteinuria persisted for only two days in patients Bra and Lai, while in patient Wea proteinuria persisted until 157 days after onset. Patients Jan and Mar had 3 plus and 4 plus proteinuria when last studied fifty-five and 100 days, respectively, after onset. In contrast to proteinuria, microscopic hematuria was still present at the end of observation in eight of ten patients.

In summary, from the clinical aspects, eight of ten patients represented a fairly homogeneous group. Within a few days of a pharyngitis, proteinuria and considerable hematuria developed but usually they did not have edema, hypertension or renal functional impairment. Proteinuria

TABLE VI
GREAT LAKES NEPHRITIS GROUP
RENAL BIOPSY DATA

Patient	Date	Days After Onset	Biopsy		Urine at Time of Biopsy		
			Length (mm.)	Glomeruli	Protein	Red Blood Cells (per high power field)	Casts
Arc.....	4–18	24	6.5	30	1+	Occasional	0
	5–25	61	6.0	23	0	0	0
Bra.....	4–18	10	5.0	17	0	10	Occasional granular
	5–25	47	3.0	7	0	0	0
Gol.....	3–14	8	6.0	10	1+	Gross	Many cellular
	5–23	78	7.0	13	0	0	0
Jan.....	7–25	44	11.0	31	3+	3–5	Occasional granular
	9–19	100	3.0	8	4+	3–5	0
Kee.....	5–16	59	6.0*	1	0	100	Rare granular
Lai.....	4–24	28	3.0	9	2+	30	Rare hyaline
	5–25	54	10.0*	12	0	10	0
Mar.....	8–13	30	2.0	0	2+	20–30	0
	9–19	71	12.0	10	3+	0–3	0
Nic.....	3–20	30	3.5	6	0	Many	Rare granular
	5–18	71	7.0*	8	0	Many	Occasional granular
Smi.....	3–28	77	5.0	21	0	20–40	Occasional granular
	5–18	143	7.5*	11	0	20–40	Occasional granular
Wea....	3–14	38	13.0	12	0	Occasional	Occasional granular
	5–23	108	8.0	21	1+	10–15	0

* Medulla present.

cleared rather promptly but microscopic hematuria persisted for several months in most patients. Patients Jan and Mar differed in that their renal disease was discovered two to three months after the others, hematuria was minimal, and proteinuria was more marked and persisted at high levels. In patient Jan the nephrotic syndrome appeared to be developing towards the end of our observations. Renal biopsies in these two patients revealed lesions which also differed from the rest of the group.

Renal Biopsies. Great Lakes Group. Renal biopsies were performed in all patients according to the technic of Kark and Muehrcke [*37*]. No

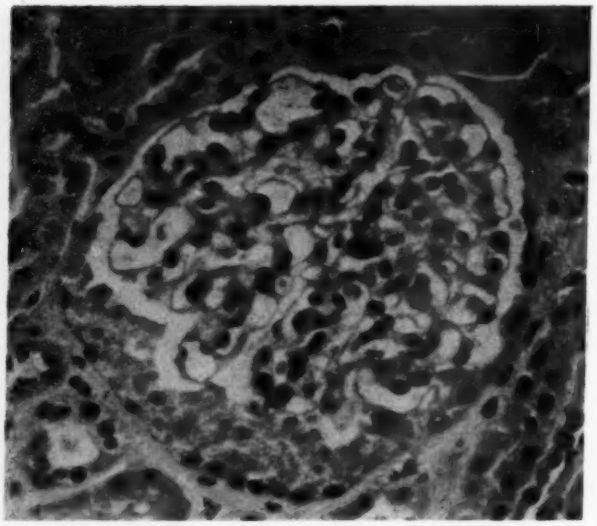

Fig. 1. A representative glomerulus from the first biopsy on Arc. Bowman's space contains protein precipitate. Note that the glomerulus is not hypercellular. The afferent arteriole of this glomerulus is normal. Hematoxylin and eosin stains, 2 micron section. Original magnification, × 446.

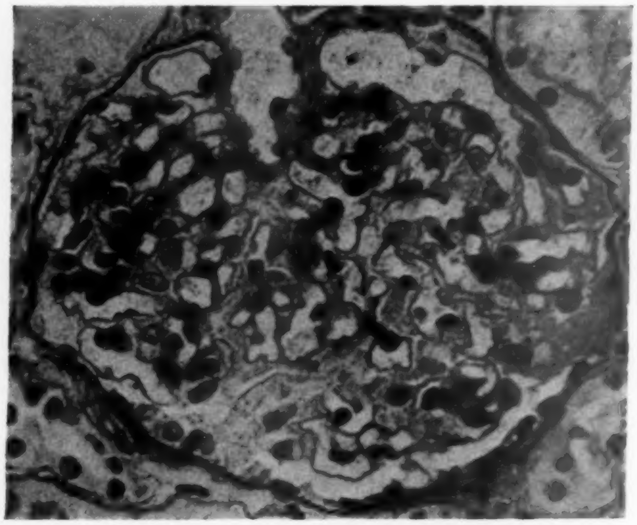

Fig. 2. A representative glomerulus from first biopsy on Bra. Except for a small focus of hypercellularity of doubtful significance, it appears normal. Periodic acid-Schiff stain, 2 micron section. Original magnification, × 216.

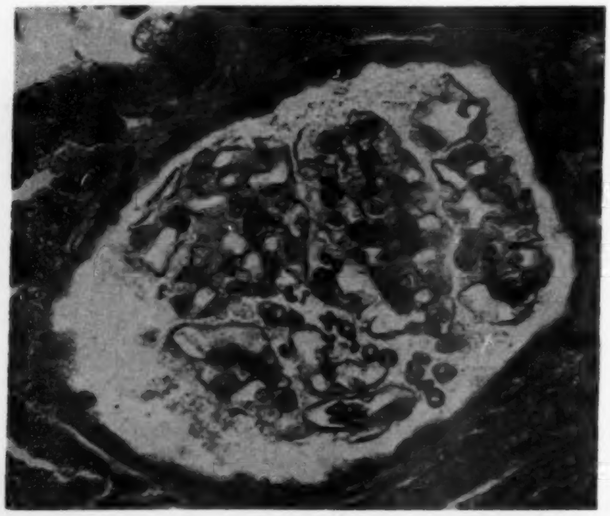

Fig. 3. Glomerulus from first biopsy on Gol showing erythrocytes in Bowman's space. Note the lack of hypercellularity. Heidenhain's stain, 6 micron section. Original magnification, × 480.

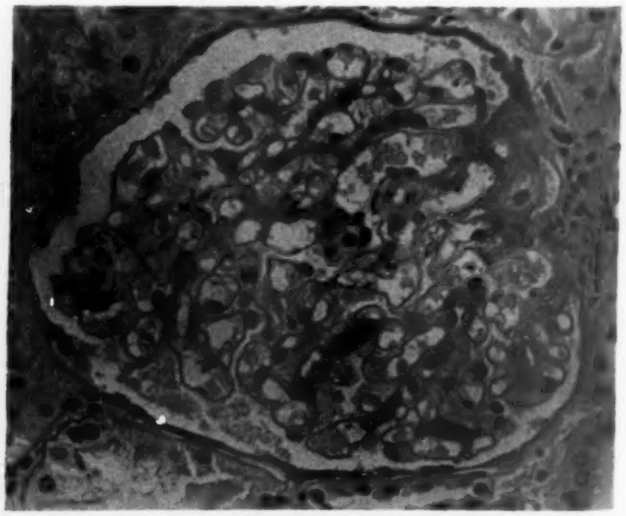

Fig. 4. Glomerulus from first biopsy on Gol stained by the periodic acid-Schiff method to show the normal structure of the basement membrane of the capillary loops. Periodic acid-Schiff stain, 2 micron section. Original magnification, × 288.

discomfort or complications occurred in this group. Specimens were fixed in Zenker-formalin solution for three hours followed by overnight washing in running tap water. After washing, they were dehydrated and embedded in paraffin. Sections were cut at 2 and 6 microns, and were stained routinely with hematoxylin and eosin, Heidenhain's modification of Mallory's connective tissue stain [*38*] and by the periodic acid-Schiff method [*39*]. Cultures of material obtained on biopsy were made in Difco brain-broth infusion medium. All cultures were sterile.

Data concerning the renal biopsies are summarized in Table vi. The initial renal biopsies were performed from eight to seventy-seven days after the onset of nephritis. Specimens of renal cortex containing adequate numbers of glomeruli were obtained from all patients but Kee, whose biopsy material consisted mainly of

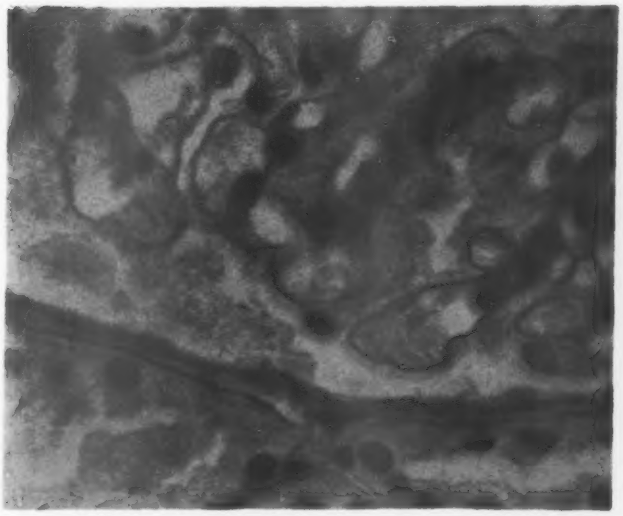

FIG. 5. Higher magnification of capillary loops of lower half of Figure 4. Loops are widely patent and basement membranes are thin and intact. Periodic acid-Schiff stain, 2 micron section. Original magnification, × 864.

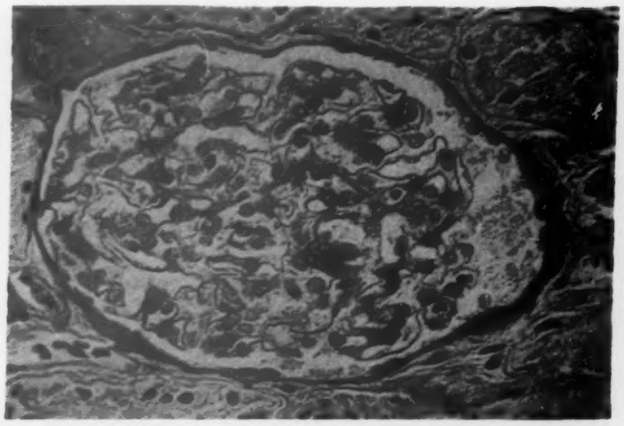

FIG. 6. Glomerulus from first biopsy on Lai. The structure of this glomerulus is slightly distorted due to lateral compression. The capillary loops are widely patent. Some protein precipitate is present in Bowman's space. Periodic acid-Schiff stain, 2 micron section. Original magnification, × 280.

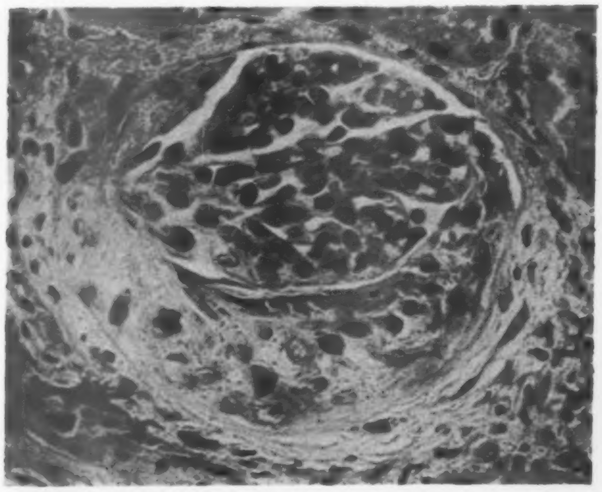

FIG. 7. Crescent in a single glomerulus from first biopsy on Nic. Hematoxylin and eosin stain, 6 micron section. Original magnification, × 460.

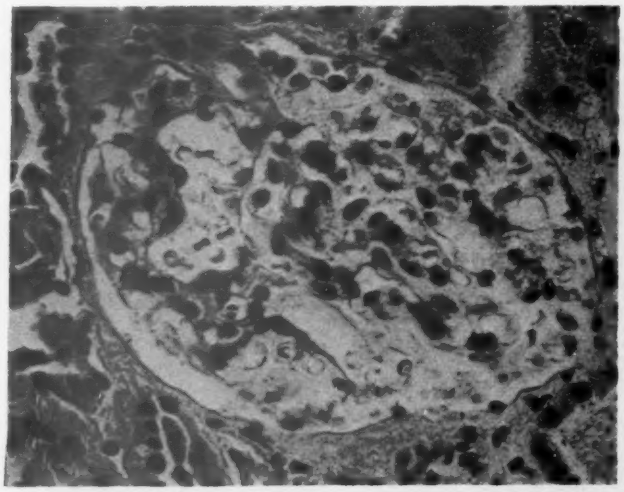

FIG. 8. Glomerulus from first biopsy on Nic showing a few erythrocytes in Bowman's space. Capillary defect through which erythrocytes passed is not visible here. Note there is no increase in cellularity. Hematoxylin and eosin stain, 6 micron section. Original magnification, × 460.

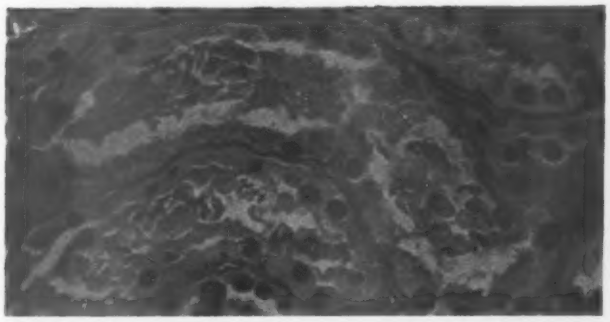

FIG. 9. Erythrocytes in the lumen of tubules in the first biopsy on Bra. Section stained by periodic acid-Schiff method which does not stain red cells thus they appear pale and refractile. Upper tubule is a dilated proximal tubule. A remnant of the brush border is apparent on the lower right. Lower tubule is a part of the ascending limb of Henle's loop. 2 micron section. Original magnification, × 630.

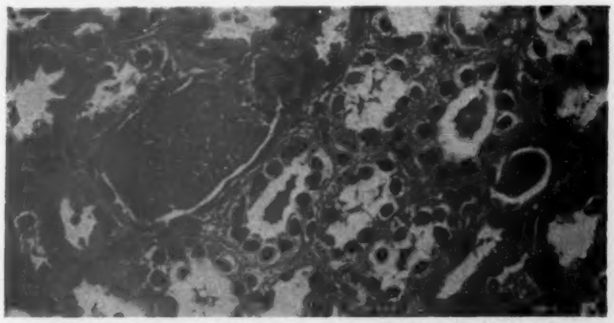

FIG. 10. Red cell cast in a tubule in the medulla of Nic's second biopsy specimen. The tubule containing the cast is probably a collecting duct but the epithelium is so flattened that it cannot be surely identified. A hyaline cast is present in a tubule on the right side of photograph. Hematoxylin and eosin stain, 2 micron section. Original magnification, × 436.

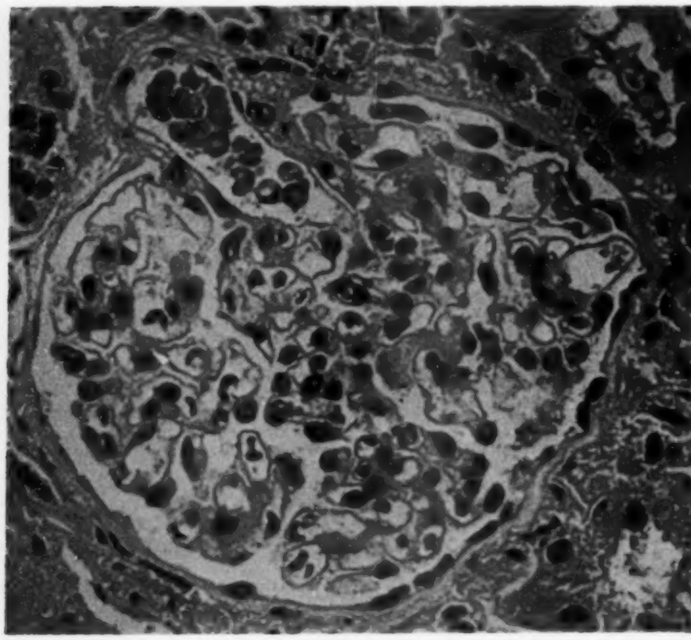

Fig. 11.

Fig. 12.

Fig. 11. Glomerulus from first biopsy on Smi showing slight focal increase in number of cells in some lobules, particularly at two and five o'clock. Afferent arteriole at top of photograph is normal. Hematoxylin and eosin stain, 2 micron section. Original magnification, × 496.

Fig. 12. A partially hyalinized glomerulus from the second biopsy on Smi. Heidenhain's stain, 4 micron section. Original magnification, × 436.

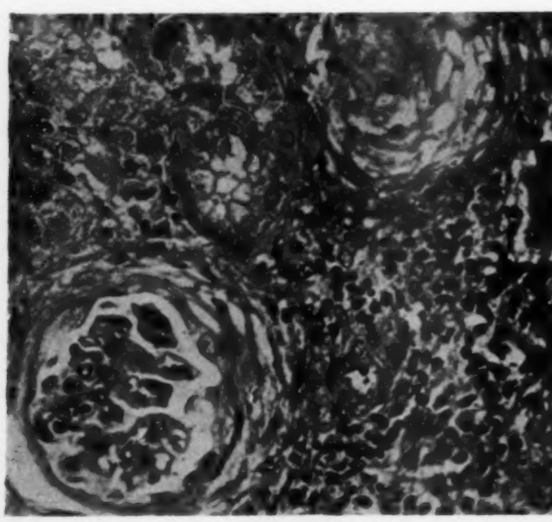

Fig. 13.

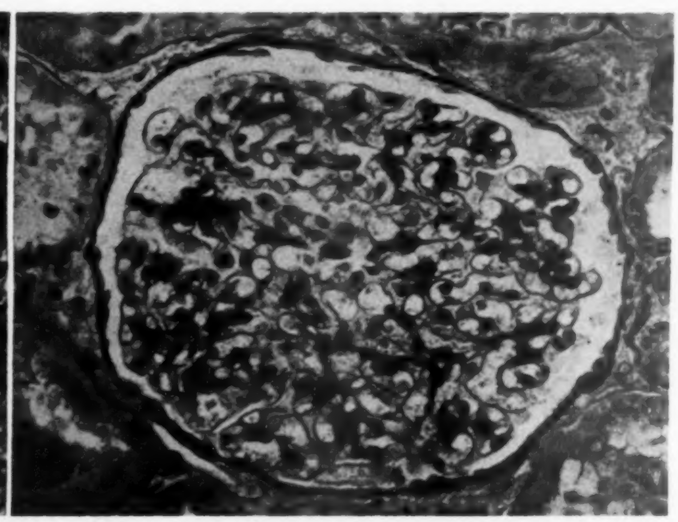

Fig. 14.

Fig. 13. A hyalinized and a partially hyalinized glomerulus from the second biopsy on Smi. Heidenhain's stain, 2 micron section. Original magnification, × 432.

Fig. 14. Glomerulus from first biopsy on Wea. Note generalized slight increase in number of cells present. Basement membranes of glomerular capillary loops are of normal thickness. Periodic acid-Schiff method with hematoxylin counterstain, 6 micron section. Original magnification, × 216.

medulla with only one normal juxta-medullary glomerulus present. For this reason, this patient will be excluded from further considerations of the renal biopsy material. Second renal biopsy specimens were obtained one to two months after the first in eight patients.

The findings in the initial biopsy specimens from patients Arc, Bra, Gol, Lai and Nic (Figs. 1–9) were similar. These five all had gross or marked microscopic hematuria at the onset of their disease. Although the first biopsy specimens from these patients were obtained within thirty days after onset, proteinuria had disappeared by the time of biopsy in patients Bra, Lai and

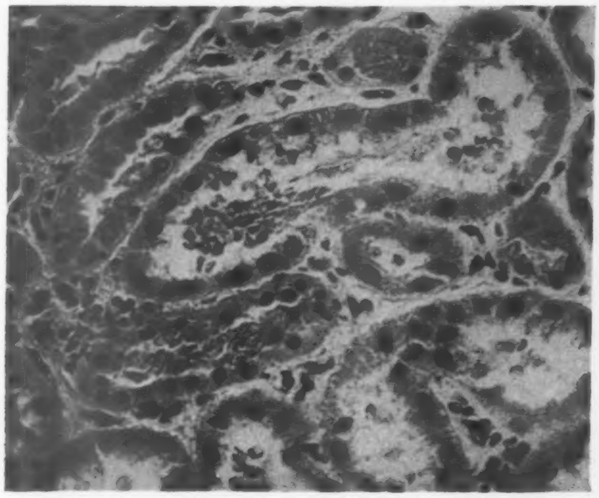

FIG. 15. Section of cortex from first biopsy on Wea showing erythrocytes in a proximal tubule and partially formed red cell casts in collecting ducts. The interstitial tissue is edematous and contains some inflammatory cells. Hematoxylin and eosin stain, 6 micron section. Original magnification, × 436.

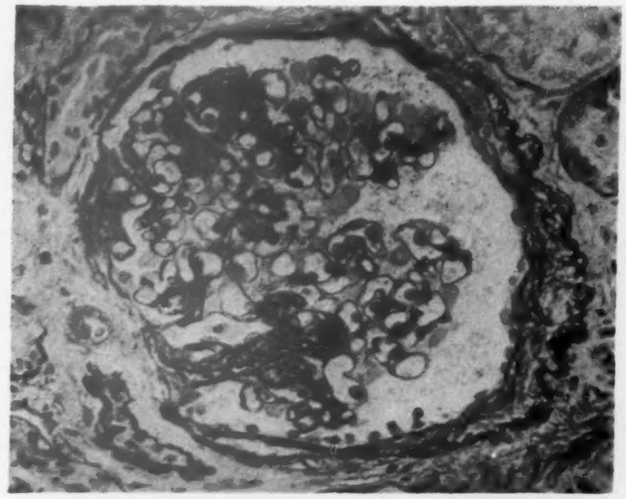

FIG. 16. Partially hyalinized glomerulus from second biopsy on Mar. Collagenous tissue stains deep red by the periodic acid-Schiff method and appears as dark black foci in mesangium of some lobules. A sclerotic arteriole of this glomerulus is in the lower left hand corner. Periodic acid-Schiff with hematoxylin counterstain, 2 micron section. Original magnification, × 480.

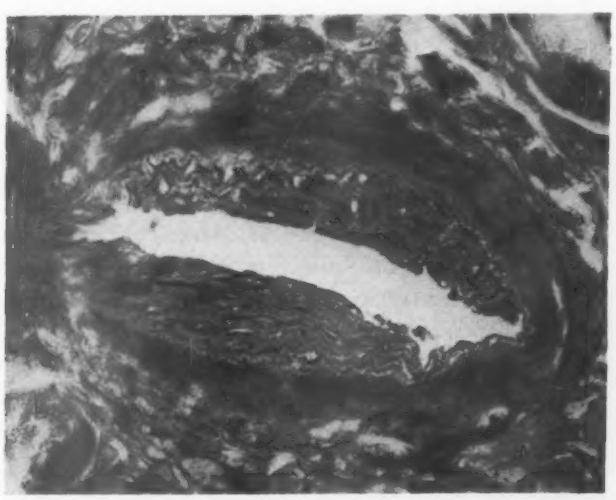

FIG. 17. Connective tissue stain of a small muscular artery from Mar's second biopsy. The internal elastica is present as a wrinkled refractile line between the intima and muscularis. Note the subintimal layer of fibrous tissue. 6 micron section. Original magnification, × 480.

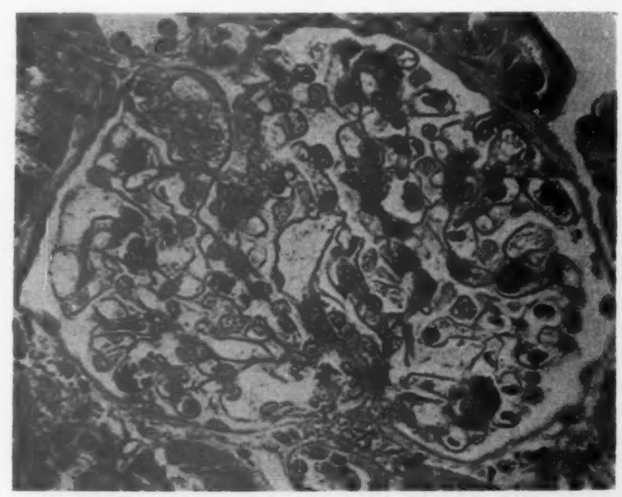

FIG. 18. Glomerulus from first biopsy of Jan showing lobules adherent to Bowman's capsule at two and eleven o'clock. The lobule at eleven o'clock contains macrophages with vacuolated cytoplasm (lipid ?). Examination of adjacent serial sections showed the arterioles of this glomerulus to be structurally normal. Heidenhain's stain, 2 micron section. Original magnification, × 640.

Nic. Gross or microscopic hematuria, however, was present in all at the time of biopsy. The most significant histologic feature was the lack of glomerular hypercellularity or inflammatory cell infiltration. The basement membranes of the capillary loops were normal. However, some degree of capillary injury not recognizable with the light microscope must have been present because red blood cells were noted in Bowman's space (Figs. 3, 8 and 9) and/or in the tubules in all except Lai. In addition, all these patients had protein precipitate in Bowman's space of some of the glomeruli. (Figs. 2–6 and 8.) A crescent was noted in a single glomerulus of patient Nic (Fig. 8) but the remaining glomeruli were indistinguishable from those found in the

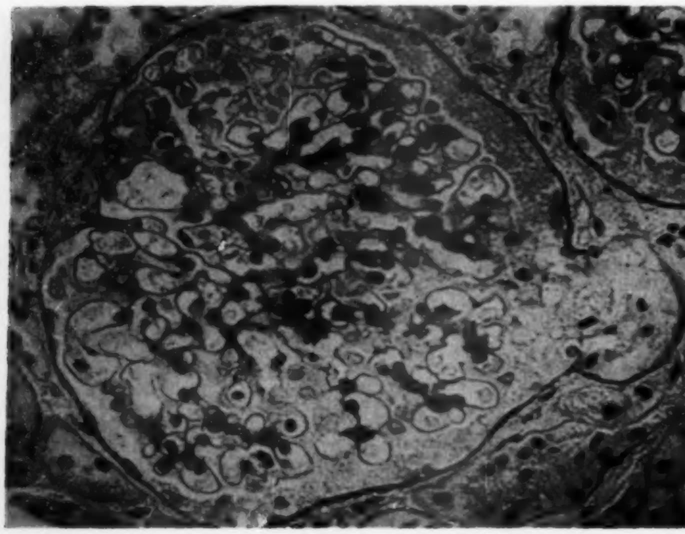

FIG. 19.

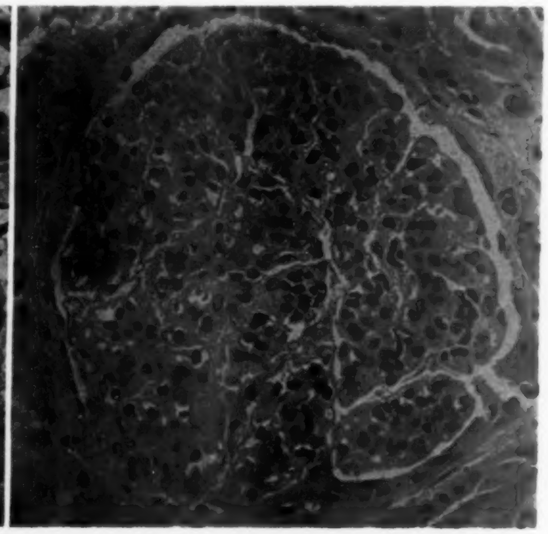

FIG. 20.

FIG. 19. A glomerulus from Jan's first biopsy. Note that it does not have the adhesive lesion shown in Figure 18. Aside from the protein precipitate in Bowman's space, this glomerulus is normal. Periodic acid-Schiff method with hematoxylin counterstain, 2 micron section. Original magnification, × 528.

FIG. 20. Glomerulus from a patient four weeks after the onset of acute glomerulonephritis following a sore throat of group A hemolytic streptococcal etiology. Note the marked hypercellularity. The increase in cells is sufficient to almost completely obscure the lumens of the glomerular capillary loops. Hematoxylin and eosin stain, 2 micron section. Original magnification, × 375.

other patients. The arterioles and arteries were normal. The proximal and distal tubules were normal except where the epithelium was flattened around red cell casts. Gol was the only patient in this group with any interstitial inflammatory reaction. A tiny focus of subacute inflammation was present in the interstitial tissue adjacent to a medium-sized muscular artery.

The second biopsy specimens from patients Arc, Bra, Gol, Lai and Nic were similar to the first except that no red cells were noted in Bowman's space of any of the glomeruli. Occasionally red blood cell casts were present in collecting ducts in Gol and Nic. (Fig. 10.) Except for several tiny foci of fibrosis in Gol, the interstitial tissue was normal. No vascular disease was observed in any of the sections. No scarred glomeruli or fibrosis of Bowman's capsule was noted in any of the patients including Nic, who had a crescent in his first biopsy. By the time the second biopsy was performed the urine had become completely normal in patients Arc, Bra and Gol; none had proteinuria; and only Lai and Nic had microscopic hematuria.

Two other patients, Smi and Wea, entered the hospital with gross hematuria as a presenting symptom. However, their renal biopsy specimens showed a histologic picture different from that of the previously discussed patients. These findings will be described separately. Clinical observations on patient Smi differed from the rest of the group in that the initial streptococcal antibody measurements were made in the thirteenth week after onset of his disease. Nevertheless, the rather low titers at this time suggested that a recent hemolytic streptococcal infection was quite unlikely. Patient Wea had more severe impairment of renal function than the rest of the group. Furthermore, Wea was the only patient whose antibody studies suggested a recent hemolytic streptococcal infection. The latent period between infection and onset of disease in this patient, however, was only one day, which would be unusually short for acute nephritis associated with streptococcal infections.

The first biopsy specimen from Smi was obtained seventy-seven days after admission. (Fig. 11.) The glomeruli were different from the first five patients described in that some small foci of hypercellularity were present in one or more lobules of each glomerulus. In addition, a hyalinized glomerulus surrounded by a tiny area of interstitial fibrosis containing chronic inflammatory cells as well as a partially hyalinized glomerulus (Fig. 12) was noted. There were no red cells in Bowman's space or in the tubular lumens. The second biopsy specimen from Smi was obtained sixty-six days after the first. Most of the glomeruli showed the slight focal hypercellularity similar to that noted in the first

biopsy, and there was another larger focus of chronic inflammation with fibrosis and chronic inflammatory cell infiltration in the cortex. (Fig. 13.) Two glomeruli were present in this focus, one completely fibrotic and the other undergoing fibrosis. Atrophic tubules containing hyaline casts were also present around these glomeruli. No vascular disease was noted in either biopsy.

The first biopsy specimen from Wea was obtained thirty-eight days after onset of his disease. All twelve glomeruli in the section showed a slight focal increase in the number of cells present. (Fig. 14.) Red cells were present in Bowman's space in some glomeruli, as was protein precipitate. The proximal tubules were normal. However, red cells were present in the lumens of several tubules, and in one area of the cortex there was a subacute interstitial inflammatory reaction. (Fig. 15.) Erythrocyte casts were present in the tubules and some proximal tubules in this area were lined with a flattened regenerative type of epithelium. In the juxtamedullary region there was another focus of interstitial fibrosis. Numerous chronic inflammatory cells, chiefly lymphocytes and macrophages, were present in this area. The second biopsy specimen from Wea was obtained seventy days later. The glomeruli were unchanged from the first biopsy except that the mesangium appeared slightly thickened in some lobules. Slight hypercellularity persisted. Bowman's space of several glomeruli contained much protein precipitate but no erythrocytes. A small focus of interstitial fibrosis was present in the cortex. It contained no inflammatory cells. The tubules in this area were atrophic and had thickened basement membranes. Another much smaller focus of inflammatory cell infiltration was noted adjacent to a small diseased interlobular arteriole. The wall of this arteriole was thickened and contained homogeneous PAS-positive hyaline material. No other arteriolar or arterial disease was observed. The proximal tubules were all normal. Except for the presence of several hyaline casts, the distal tubules were normal.

Mar and Jan differed from all the other patients in the Great Lakes group in that they entered the hospital two and three months, respectively, after the first group and did not have marked hematuria as a presenting sign. Their proteinuria was greater than that observed in the others.

The first biopsy attempt on Mar was unsuccessful. All that was obtained was a single crushed glomerulus enmeshed in blood clot. The second biopsy specimen was obtained 101 days after the onset. His urine sediment at this time was unchanged from admission. All the glomeruli were normal except for one which was partially hyalinized. (Fig. 16.) The afferent arteriole of this glomerulus was sclerotic and the adjacent parenchyma partially hyalinized. Although this patient was only seventeen years old, the intima of a large muscular artery in the biopsy specimen was markedly sclerotic. (Fig. 17.) The proximal and distal tubules were normal except for occasional hyaline casts noted in some distal tubules.

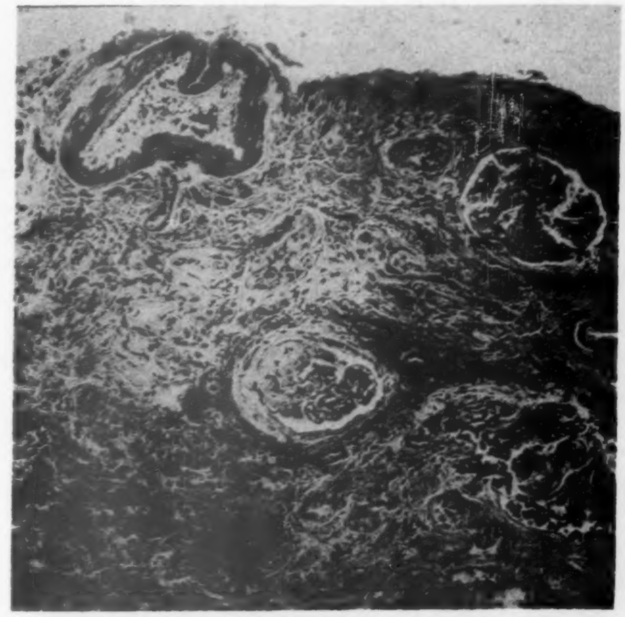

FIG. 21. Renal biopsy specimen from a patient three months after the onset of acute glomerulonephritis which followed a group A hemolytic streptococcal sore throat. Note the two partially hyalinized glomeruli and the severe interstitial fibrosis. Heidenhain's stain, 6 micron section. Original magnification, × 131.

A few glomeruli in the first biopsy specimen from Jan showed a focal glomerular lesion not observed in any of the other patients. Some lobules in these glomeruli were fibrotic and adherent to Bowman's capsule. In the mesangium of one of these lobules there were macrophages with vacuolated cytoplasm. (Fig. 18.) In this respect these glomeruli differed from all others in the series. The basement membranes of the capillary loops of the uninvolved lobules of the diseased glomeruli were normal. No abnormalities other than protein precipitate in Bowman's space of some glomeruli were noted. (Fig. 19.) Hyaline droplets which stained with

TABLE VII
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS IN REGARD TO INFECTION
(NUMBER POSITIVE/NUMBER EXAMINED)

Group	Penicillin Prophylaxis	Infection	Hemolytic Streptococci on Throat Culture	Temperature 101°F. (orally)	White Blood Cells > 9,000/cu. mm.	Erythrocyte Sedimentation Rate >20 mm./hr.
Great Lakes.......	5/10	9/10	...	5/10	2/10	3/9
Streptococcal......	0/11	9/11	5/6	5/8	6/6	6/6

the periodic acid-Schiff method were present in the cytoplasm of almost all the proximal tubular cells. Hyaline casts were present in the lumens of some of the distal tubules. The arterioles and arteries were all normal. The second biopsy specimen included a portion of renal capsule and eight subcapsular glomeruli. No lesions were observed in any of these glomeruli and the proximal tubules and arteries were also normal even though the patient still had heavy proteinuria and the nephrotic syndrome appeared to be developing.

TABLE VIII
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. INCIDENCE OF SERUM ANTIBODIES AGAINST HEMOLYTIC STREPTOCOCCI
(NUMBER INCREASED/NUMBER ADEQUATELY OBSERVED)

	No. of Patients	ASO	ASK	AH	Any of 3*	Type 12
Great Lakes........	10	1/9	1/9	0/8	1/9	1/10
Streptococcal.......	11	7/8	7/8	4/5	8/9	6/11

NOTE: ASO = antistreptolysin titer.
ASK = antistreptokinase titer.
AH = antihyaluronidase titer.
Adequate observation was considered to consist of either an initial observation within two months of the onset of the disease or significant serial decrease in titers.
* Increase in at least one of the ASO, ASK and AH antibody titers.

In summary, adequate renal biopsy specimens were obtained in nine of ten patients. Five of these were similar in that they showed little overt glomerular disease except for the presence of a crescent in one patient. However, red blood cells in Bowman's space and/or in the lumens of the tubules were found in all. Repeat biopsies in this group showed no additional abnormalities. Two other patients with similar clinical findings differed on biopsy from the others in that slight hypercellularity was present in some of the lobules of all glomeruli seen. The remaining two patients, Jan and Mar, differed clinically from the others. Likewise, their renal biopsies differed from the rest of the group. A focal apparently chronic glomerular lesion of unknown origin was observed in Jan, while Mar had several glomeruli undergoing fibrosis, apparently related to arteriolar and arterial sclerosis. Most of the glomeruli of these two patients, however, appeared to be normal.

TABLE IX
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. LATENT PERIOD BETWEEN INFECTION AND ONSET OF NEPHRITIS

Group	No. of Patients	5 Days or Less	6 Days or More	Unknown
Great Lakes......	10	9	0	1
Streptococcal.....	11	0	8	3

Acute Nephritis of Great Lakes Outbreak Compared to Acute Glomerulonephritis Contracted Elsewhere. During the period of the Great Lakes outbreak we studied in a similar fashion eleven patients with acute glomerulonephritis contracted elsewhere. Bacteriologic and/or immunologic evidence of a recent hemolytic streptococcal infection was obtained in all the latter patients. These patients will subsequently be referred to as the "streptococcal" group. A number of distinctive differences were observed between the two groups. These differences are summarized in Tables VII to XIII. The details of our studies on

TABLE X
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. CLINICAL FEATURES

Group	No. of Patients	Edema	Hypertension	Gross Hematuria	Impaired Renal Function	Blood Urea Nitrogen >20 mg. %
Great Lakes	10	3	1	7	1	1
Streptococcal	11	7	7	2	9	8

the patients with acute glomerulonephritis following hemolytic streptococcal infections will be presented in another paper [*40*].

When evaluating the comparison of the findings between the two groups, the reader should be reminded that the patients with nephritis contracted in locations outside the Great Lakes Naval Station represent a selected group in part, since six had been transferred to the Great Lakes Naval Hospital because their disease had not healed promptly. Further, details concerning the associated infections and the onset of the acute nephritis in these six patients were not observed at first hand by us. Finally, the hemolytic streptococcal group included four patients aged thirty years or more.

TABLE XI
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. DURATION OF PROTEINURIA AND HEMATURIA

Group	Total No. of Patients	No. Patients With Duration More Than 100 Days	
		Proteinuria	Hematuria
Great Lakes	10	2	7
Streptococcal	11	7	7

Associated overt infections occurred in all but one patient in each group. (Table VII.) In contrast to the Great Lakes nephritis group who had only pharyngitis and in one instance complicating pneumonitis, two patients in the streptococcal group suffered from severe tonsillitis and cervical adenitis, one had acute rheumatic fever, one had erythema multiforme and one had Henoch-Schoenlein purpura. Patient Smi had hyperthyroidism with a basal metabolic rate of +65 per cent when first observed. This responded to antithyroid medication. Data on white blood cell counts were obtained during active infection in seven of the streptococcal patients. The counts ranged between 11,200 and 19,700 per cu. mm. Throat cultures were reported for seven patients, hemolytic streptococci being found in six. One of these strains was typed and found to be type 12.

Serial observations on ASO, ASK and AH titers yielded definite evidence of recent hemolytic streptococcal infections in eight of the streptococcal group. (Table VIII.) The first serum for antibody studies was not obtained in one patient until the seventh month after infection. All antibody titers were in the normal range. However, group A hemolytic streptococci had been recovered from a throat culture at the onset of his acute glomerulonephritis. The remaining patient, whose serum antibodies were first measured ten weeks after his pharyngitis, had ASO titers of borderline significance (166 to 200 units). However, his serum contained type 12 antibodies in high titer twelve weeks after infection. Another patient, whose ASO titers (125 to 200 units) and ASK titers (320 to 640 units) were of borderline significance, had a strongly positive test for type 12 antibodies and had had a throat culture positive for hemolytic streptococci at the onset of his nephritis. Thus, all the eleven patients in whom acute nephritis developed elsewhere had definite or presumptive evidence of a recent hemolytic streptococcal infection in contrast to only one of ten patients in the Great Lakes group. Six of the eleven streptococcal patients had type 12 antibodies in contrast to one of ten in the Great Lakes outbreak.

Perhaps the most striking clinical difference between the two groups (Table IX) was the short latent period between the onset of infection and

the first sign of renal disease, which did not exceed five days in the Great Lakes nephritis group but which averaged ten days in the others. As shown in Table x, gross hematuria was more common while hypertension and edema were less common in the Great Lakes patients as compared to the other group. Likewise, impairment of renal function was not present or was minimal among the Great Lakes patients, only one having a blood urea nitrogen value greater than normal. In contrast, eight of the eleven other patients had blood urea nitrogen values greater than 20 mg. per cent. Although the majority of patients in both groups still had microscopic hematuria at the end of the period of observation, proteinuria ceased in all but two of the Great Lakes patients but was still present at the time of last examination in seven of the eleven streptococcal patients. (Table xi.) Since disappearance of protein from the urine even in the presence of continued hematuria generally is accepted as evidence of healing of acute glomerulonephritis [4], the majority of the Great Lakes patients presumably will achieve a clinical cure of their disease. However, six of the streptococcal patients still had proteinuria six months or more after onset of acute glomerulonephritis. Most of these patients probably will not be cured. Indeed, serial renal biopsies in these patients indicated the presence of relatively severe and persistent glomerulonephritis many months after onset of their disease (*vide infra*). The data compared in this paragraph must be interpreted with the knowledge that the patients who contracted their disease elsewhere were not an entirely unselected group.

TABLE XII
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. INITIAL SERUM PROTEIN PAPER ELECTROPHORETIC PATTERNS

Group	No. of Patients	Albumin, % of Total		Gamma Globulin, % of Total	
		<45	>45	<25	>25
Great Lakes...	10	4	6	9	1
Streptococcal..	7*	5	2	3	4

* Excluding four patients whose initial studies were made late in the course of their disease.

TABLE XIII
COMPARISON BETWEEN GREAT LAKES AND "STREPTOCOCCAL" ACUTE NEPHRITIS GROUPS. MINIMUM SERUM COMPLEMENT

Group	Serum Complement (units)		
	<25	25–35	>35
Great Lakes.........	1	7	2
Streptococcal........	3	5	3

NOTE: Normal serum complement = 40 to 50 units.

Paper electrophoretic analysis of serum proteins (Table XII) revealed greater alterations among the patients in the streptococcal group than among those in the Great Lakes nephritis group. Serum complement (Table XIII), however, behaved similarly in the two groups, being reduced for many weeks in the majority of patients.

The histologic changes seen on renal biopsy were much more severe in the streptococcal group than among the Great Lakes patients. Biopsies were performed within a month of the onset of acute glomerulonephritis in four patients whose disease was associated with group A streptococcal infection. In two, glomerular hypercellularity, although definite, was only slightly more obvious than that observed in patient Wea (Fig. 14) who represented the most marked example of this feature among the Great Lakes patients. The other two early biopsies in the streptococcal patients revealed classic acute diffuse glomerulonephritis (Fig. 20) as described by Bell [29] and others. The first renal biopsy specimens from the other patients in the streptococcal group were obtained from one to four months after the onset of nephritis. Two of these patients had severe acute glomerulonephritis as judged by the first biopsies, and showed glomerular scarring and severe tubular and interstitial changes in a second biopsy performed several months later. Many of the remaining patients had changes typical of chronic glomerulonephritis revealed in one or more renal biopsies. (Fig. 21.) All but two patients in the streptococcal group had markedly hypercellular glomeruli. In contrast, none of the Great Lakes patients exhibited histologic evidence of typical diffuse glomerulonephritis, and only one had unequivocal glomeruli hypercellularity.

COMMENTS

A small outbreak of acute nephritis associated with pharyngitis occurred at the Great Lakes Naval Training Center during the winter and spring months of 1956. Gross hematuria, present in seven of ten patients studied, was an outstanding clinical feature. All patients had proteinuria and casts as well as erythrocytes in the urinary sediment, but edema, hypertension and impairment of renal function were uncommon.

Anatomic damage in the kidneys as revealed by renal biopsies was less severe and persistent than that which was found in eleven other patients observed by us during the same period of time whose attacks of acute glomerulonephritis were contracted elsewhere and were associated with group A hemolytic streptococcal infections.

Likewise, prognosis appeared to be better among the Great Lakes patients than among the patients whose nephritis followed hemolytic streptococcal infections. However, acute diffuse glomerulonephritis following hemolytic streptococcal infections, especially in epidemics, is frequently characterized by a benign course and a good prognosis [*4*].

Sufficient data are not at hand to state that all mild instances of "streptococcal" acute nephritis are characterized by increased glomerular cellularity and therefore differ basically from the minimal lesions of the glomeruli in the Great Lakes patients. In a renal biopsy study of twelve patients with acute glomerulonephritis, Gormsen and colleagues [*41*] describe the histologic findings in seven mild to moderately severe cases in which renal function was normal or only slightly reduced. They found slight to moderate hyalinizations in the glomeruli and varying degrees of endothelial and epithelial proliferation. Two of our streptococcal patients had little or no impairment of renal function. These patients did exhibit some but not marked glomerular hypercellularity.

One of the striking features of the Great Lakes outbreak was the short latent period between the associated infection and onset of the signs of nephritis. The latent period in classic acute glomerulonephritis following group A hemolytic streptococcal infections is generally one to four weeks [*42*]. In contrast, the latent period in the Great Lakes patients did not exceed five days. Indeed, gross hematuria preceded the symptoms of the associated pharyngitis in two patients by one and by three days. A short latent period is characteristic of the exacerbation in chronic glomerulonephritis [*3,42,43*]. However, several considerations make underlying chronic glomerulonephritis most unlikely among the Great Lakes patients. They were all young recruits who presented no evidence of prior renal disease or symptoms. Presumably urinalyses on admission to the Navy were normal. Most important, proteinuria cleared in eight of the ten patients. Finally, only one of the ten patients had any evidence of a recent hemolytic streptococcal infection, while approximately 70 per cent of exacerbations in chronic glomerulonephritis follow streptococcal infections [*43*].

In addition to the latent period, and despite the lack of adequate bacteriologic studies, several other lines of evidence strongly suggest that the Great Lakes outbreak of acute glomerulonephritis was not associated with group A hemolytic streptococcal infections. In the first place, the outbreak occurred at a time when the training camp personnel was receiving penicillin prophylaxis and very few streptococcal infections were developing. Five of ten patients with acute nephritis had received penicillin prophylaxis within one to four weeks of the onset of this disease. Although nine patients had pharyngitis, with temperatures ranging from 100° to 104°F., in none did polymorphonuclear leukocytosis or cervical adenitis develop. Most important, serial ASO, ASK and AH serum titers could be interpreted as evidence for a recent hemolytic streptococcal infection in only one patient. The latter was the only patient in the group who had sufficient renal functional impairment to result in nitrogen retention. Further, the findings on renal biopsy in this patient were more severe than in the others in the group and more closely resembled the histologic changes seen in those patients whose nephritis was demonstrated to follow hemolytic streptococcal infections. Nevertheless, the latent period in this patient was only one day, unusually short for the initial attack of acute glomerulonephritis following a hemolytic streptococcal infection.

We believe, on the basis of the evidence discussed, that the outbreak of nephritis observed at the Great Lakes Naval Training Station was not related to group A hemolytic streptococcal infections, with the possible exception of one patient. Although we have no positive evidence, we suspect on clinical grounds that the associated infections were probably viral in origin. One pa-

tient (Gol) had a complicating pulmonary lesion which clinically and radiographically appeared to be viral pneumonitis. In none of the patients did cold hemagglutinins develop. Upper respiratory infections due to adenoviruses were common at the training station during the time of outbreak of acute nephritis. Throat washings from five patients and renal biopsy material from one patient did not yield adenovirus. Several textbooks state, without presenting evidence, that acute glomerulonephritis may follow a variety of infections including those of virus etiology. However, the only well established instances of acute glomerulonephritis associated with viral infections found in a review of the literature included two following vaccination for smallpox [*24,25*] and one associated with infectious mononucleosis [*23*]. No evidence of recent hemolytic streptococcal infections was reported in the protocols of these patients but throat cultures and serum antibody studies were not made.

Decreased serum complement has been used as evidence for an antigen-antibody pathogenesis of acute glomerulonephritis of the ordinary variety following group A hemolytic streptococcal infections [*44–46*]. Serum complement was decreased in the Great Lakes nephritis group, often for many weeks after proteinuria had cleared and in the absence of any obvious histologic evidence of glomerular damage. The significance of the decreased serum complement in these patients is not clear, although it is tempting to assume that it is evidence that the Great Lakes nephritis had an antigen-antibody pathogenesis.

Since some of the Great Lakes patients received penicillin prophylaxis, the possibility of a renal manifestation of an allergic response to the drug should be considered. However, gross hematuria and proteinuria which persisted for more than a few days in the absence of other more common manifestations of a penicillin reaction would be most unusual. Furthermore, pharyngitis is not a feature of a penicillin reaction and the coincidental occurrence of pharyngitis and renal manifestations of a penicillin reaction in nine (one of ten had no pharyngitis) unselected patients with signs of acute glomerulonephritis is statistically unlikely. Finally five patients had not received penicillin prophylaxis. Although five patients were treated with antibiotics for their pharyngitis (three received terramycin®, one penicillin and one gantrisin®), the latent period in these patients was so short that the therapy was instituted after the onset of the acute nephritis in four. In none of the patients did an eosinophilia develop.

Focal non-suppurative glomerulonephritis is said to occur at the height of a variety of infections [*5,29,47*] and may be associated with chemical poisons and reactions to therapeutic agents such as the sulfonamides [*47*]. The impression left by the literature is that the proteinuria and hematuria associated with these conditions are quite transient, generally lasting only during the febrile phase. In contrast, proteinuria in most of the Great Lakes patients persisted for several weeks or months after defervescence, and hematuria was even more persistent. Nevertheless, the renal biopsy data obtained in the Great Lakes patients strongly suggest focal lesions. The great majority of the glomeruli appeared entirely normal, yet the presence of erythrocytes in Bowman's space and in some tubules and of blood cell casts in the tubules indicate the existence of glomerular lesions, as do the proteinuria and hematuria. Perhaps, too, the occasional glomerular crescent and hyalinized glomeruli observed can be taken as evidence for a focal glomerular disease. Damage to a few glomerular capillary loops could result in proteinuria and hematuria. The renal biopsy technic, of course, permits examination of only a rather small sample of glomeruli.

It is entirely possible that the glomerular lesions in the milder instances of acute glomerulonephritis following hemolytic streptococcal infections are also focally distributed. Unfortunately, sufficient data on this point are not available to permit conclusions as to whether or not a focal distribution of glomerular lesions represents another difference between streptococcal and non-streptococcal nephritis. We believe that the Great Lakes patients suffered attacks of acute nephritis which, although the glomerular lesions were focally distributed, were examples of a specific disease of specific etiology.

SUMMARY AND CONCLUSIONS

A study is reported of an outbreak of acute nephritis involving ten patients at the Great Lakes Naval Recruit Training Center. All but one of the cases were associated with pharyngitis. Leukocytosis was not a feature of the pharyngitis. Clinical and immunologic evidence ruled out

recent group A hemolytic streptococcal infections in nine of ten patients.

Compared to a group of eleven patients whose acute glomerulonephritis developed elsewhere following group A hemolytic streptococcal infections, the Great Lakes nephritis group exhibited shorter latent periods between infection and onset of nephritis, more gross hematuria, less hypertension, less edema and less renal functional impairment.

Healing occurred during the period of observation in at least eight of the Great Lakes nephritis group, as evidenced by disappearance of proteinuria although microscopic hematuria persisted for several months or more in most patients.

Renal biopsies revealed evidence of glomerular damage in the Great Lakes group which was much milder and presumably focal in distribution as compared to more severe and proliferative changes observed in patients whose acute nephritis followed group A hemolytic streptococcal infections.

It is concluded that acute hemorrhagic nephritis can be associated with pharyngitis not of group A hemolytic streptococcal etiology.

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A Syndrome of Renal Sodium Loss and Hyponatremia Probably Resulting from Inappropriate Secretion of Antidiuretic Hormone*

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This paper is a report of studies of two patients with bronchogenic carcinoma in whom hyponatremia developed as the result of unexplained failure of renal sodium conservation. The data indicate that sustained inappropriate secretion of antidiuretic hormone was probably responsible for the disorder of sodium metabolism. The physiologic abnormality appears to be analogous to that which can be produced by the continuous administration of pitressin® and water to normal subjects.

CASE REPORTS

Case i. W. A., a sixty-year old hat cleaner, complained of coughing up bright red blood for the previous six weeks, and loss of 15 pounds of weight. On physical examination, he was well nourished. The blood pressure was 120/70 mm. Hg. There was marked clubbing of the fingers and toes which the patient said had been present all his life. Physical and neurologic examination was otherwise within normal limits.

Initial routine laboratory studies revealed no abnormalities in the hemogram. Urine examination was negative. Intravenous pyelogram revealed normal structure and excellent dye concentration in both kidneys.

X-ray revealed a 4 by 5 cm. ill-defined mass in the region of the right pulmonary artery. A biopsy by bronchoscope demonstrated anaplastic carcinoma of the right main stem bronchus, and an exploratory thoracotomy revealed an inoperable tumor at the right hilum infiltrating the esophagus and aorta. In the postoperative period empyema developed, which was satisfactorily controlled with antibiotics and saline solution irrigations. Two weeks after operation serum electrolytes and protein concentrations were measured as a routine procedure. The following values were obtained: sodium, 121 mEq./L.; potassium, 4.6 mEq./L.; chloride, 88 mEq./L.; carbon dioxide content, 24 mEq./L.; calcium, 10.0 mg. per cent; inorganic phosphate, 4.0 mg. per cent; albumin, 2.1 gm. per cent; globulin, 3.7 gm. per cent. The hemoglobin was 9.8 gm. per cent. The patient was given small amounts of normal saline solution and on the following day his serum sodium was 114 mEq./L. and his blood urea nitrogen was 9 mg. per cent. The urine sodium concentration was 70 mEq./L. At this time the physical examination was within normal limits. The blood pressure was 124/68 mm. Hg. Skin turgor and hydration were good. There was no abnormal pigmentation and axillary and pubic hair were normal. During the next two days he was given hypertonic sodium chloride, despite which his serum sodium concentration fell to 103 mEq./L. During this time the patient was asymptomatic. He was then given small doses of DOCA® and very large amounts of supplementary salt. Three days later metabolic studies were begun,

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as described under "Results." On the first day of these studies 20 mg. of DOCA were administered.

The patient was discharged from the hospital two months later. It was found that on salt intake *ad libitum* and slightly restricted fluid intake his serum sodium concentration could be maintained at normal or near normal values without steroids. During the next three months he was readmitted on two occasions for further observation. His final admission occurred eight months after the initial studies and three months after his last period of observation. He was emaciated, and had severe diarrhea and jaundice. Despite supportive therapy his condition progressively deteriorated, and he died three weeks after admission.

Autopsy revealed extensive bronchogenic carcinoma involving numerous mediastinal lymph nodes and the pericardium and invading and obscuring the vagus nerves. Metastases had obstructed the common bile duct and the pancreatic duct. There was extensive invasion of the adrenal area by metastatic tumor: the 5 to 10 per cent of the one adrenal cortex which was found was histologically normal. There were scattered metastases in the kidneys, which were otherwise grossly and microscopically normal. The brain showed metastases in the cerebral hemispheres and cerebellum, and bilateral cystic degeneration in the region of the basal ganglia. The pituitary gland was normal on gross and microscopic examination.

CASE II. W. F., a fifty-six year old prizefighter, complained of anorexia, weakness and fatigability of one year's duration. Five months before admission the symptoms rapidly became more severe, and he was admitted to an outside hospital where he was observed to have severe hyponatremia (serum sodium 105 to 116 mEq./L.). The hyponatremia persisted despite administration of large quantities of salt and was accompanied by continuous loss of sodium in the urine. There was no clinical evidence of salt depletion. The non-protein nitrogen was 26 mg. per cent, and urinalysis was negative. He was found to have a duodenal ulcer. No adequate explanation could be found for the electrolyte disturbance, and he was admitted for further studies.

On physical examination, he was found to have normal skin turgor, normal body hair and no abnormal pigmentation. The blood pressure was 200/110 mm. Hg. Physical and neurologic examination was otherwise within normal limits. The urine was normal on numerous occasions; the hemogram was normal.

Chemical analyses revealed the following serum values: urea nitrogen, 12 mg. per cent; sodium, 133 mEq./L.; carbon dioxide content, 31 mEq./L.; potassium, 5.6 mEq./L.; glucose tolerance test, fasting 92 mg. per cent, thirty minutes 181 mg. per cent; sixty minutes 158 mg. per cent, 120 minutes 65 mg. per cent. Radioactive iodine uptake was normal (44 per cent) as was the basal metabolic rate (minus 5 per cent). Alterations in serum sodium concentration and results of studies of renal and adrenal function are described under "Results."

X-ray film revealed a prominence in the left hilum, thought to be pulmonary artery, and a duodenal ulcer. The sella turcica was normal.

Metabolic studies were instituted. Shortly thereafter periods of aphasia and disorientation began to appear with increasing frequency and duration. On the fifty-eighth hospital day biparietal burr holes were made revealing normal cerebrospinal fluid pressures. During the next two weeks clouding of the sensorium became progressively deeper and more continuous, and on the seventy-first hospital day a right facial paralysis and a right hemiparesis developed. Shortly thereafter the patient lapsed into coma. On his ninety-seventh hospital day he had hypotension for the first time, and two days later he began passing large amounts of dark red blood by rectum. This persisted, and despite numerous transfusions he failed rapidly; he died on his 101st hospital day.

Autopsy revealed a bronchogenic carcinoma measuring 8 by 4 cm. extending from the arch of the aorta to the left main stem bronchus, surrounding and compressing the left pulmonary artery and vein, involving numerous hilar lymph nodes, and invading and obscuring the vagus nerves. The sole extrathoracic metastasis was a single nodule, 0.8 cm. in diameter, in the medulla of the left adrenal gland, which was otherwise normal in size and structure, as was the right adrenal. The adrenal glands together weighed 15.5 gm. There were three duodenal ulcers one of which had eroded a small artery. The kidneys were grossly normal and showed only minimal arteriosclerosis. The brain showed encephalomalacia of the left internal capsule and caudate nucleus and of the right globus pallidus, pons and hippocampus. The pituitary gland was normal on gross and microscopic examination.

METHODS

The patients were offered weighed diets which contained little sodium, but were otherwise normal in composition. Sodium chloride was added each day with weighed salt shakers in order to raise the sodium intake to the desired level. On various occasions extra sodium chloride loads were administered intravenously as 2.5 to 5 per cent solutions. In the study of W. A., 40 mEq. of potassium chloride were added to the daily intake from the seventeenth day to the end of the study. Absolute constancy of intake was impossible in W. A. because of frequent rejections of variable amounts of salt and food; and on one occasion the composition of the diet was changed. Food which was refused and vomitus were analyzed. In the studies of W. F., urinary incontinence resulted in occasional incomplete collections; losses were estimated not to have exceeded 100 cc. per day.

Measurements of inulin and p-aminohippurate clearances were made in the standard manner. The

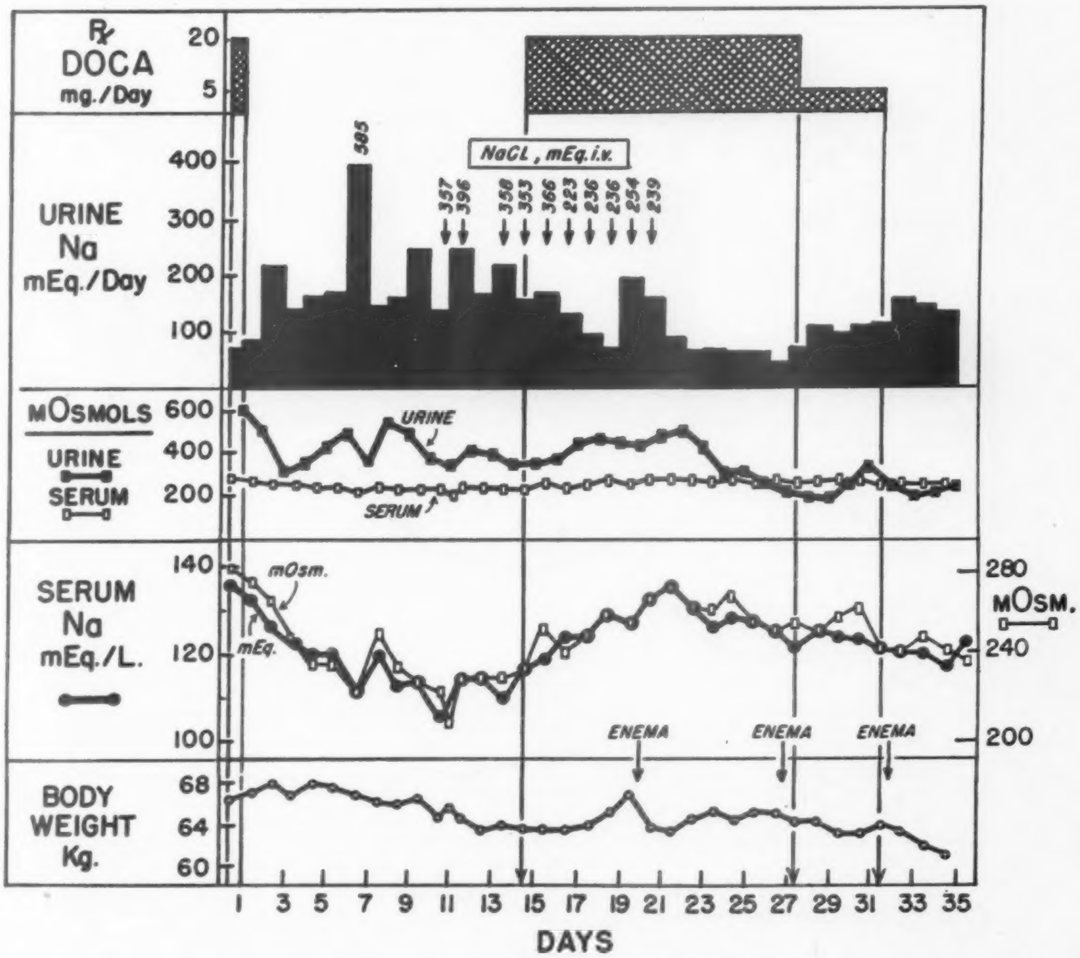

FIG. 1. Urine sodium, urine and serum osmolality, serum sodium concentration, body weight and steroid therapy during a thirty-five-day balance study of W. A. Dietary sodium intake was as follows: Days 1 to 9, 62 mEq. Days 10 to 35, 42 mEq. Supplementary sodium intake is indicated by arrows. For net intake (corrected for refusals) see Table I.

analytic procedures, the methods used in the calculations of results, and other details of the balance technic have been described previously [2,3]. Osmolality of the urine and blood was estimated from freezing point depression. 17-Hydroxycorticoids were measured with and without the administration of 40 units of ACTH intravenously over an eight-hour period. Urinary aldosterone was measured by a method previously described [4]. The radiosodium, radiosulfate and radiopotassium spaces were determined simultaneously by the method of Burrows, Hine and Ross [5].

RESULTS

Effects of Altering Sodium Intake. (*Table I and Figs. 1 and 2.*) Patient W. A. (Table I and Fig. 1) was transferred from the Surgical Service, where he had been receiving large amounts of hypertonic saline solution and 10 mg. of desoxycorticosterone acetate (DOCA) daily for three days. On the first day of the metabolic study the serum sodium concentration was 136 mEq./L. and the osmolality 282. DOCA, 20 mg., was administered on the first day and then discontinued. The patient was offered a constant diet containing 62 mEq. of sodium per day. During the first six days the serum sodium concentration fell to 108 mEq./L., and the serum osmolality to 220. During this time the urine sodium excretion rose to levels of 150 to 200 mEq. per day with a simultaneous urine osmolality of 300 to 600. The body weight at the end of this period was the same as at the beginning of the study. On day 7 the oral sodium intake was supplemented by intravenous sodium chloride to make a total of 608 mEq. On the following day the serum sodium concentration was 119 mEq./L. During the next three and a half days the serum sodium fell to 103 mEq./L. and osmolality to 202. The urine sodium ranged between 143 and 242 mEq. per day and urine

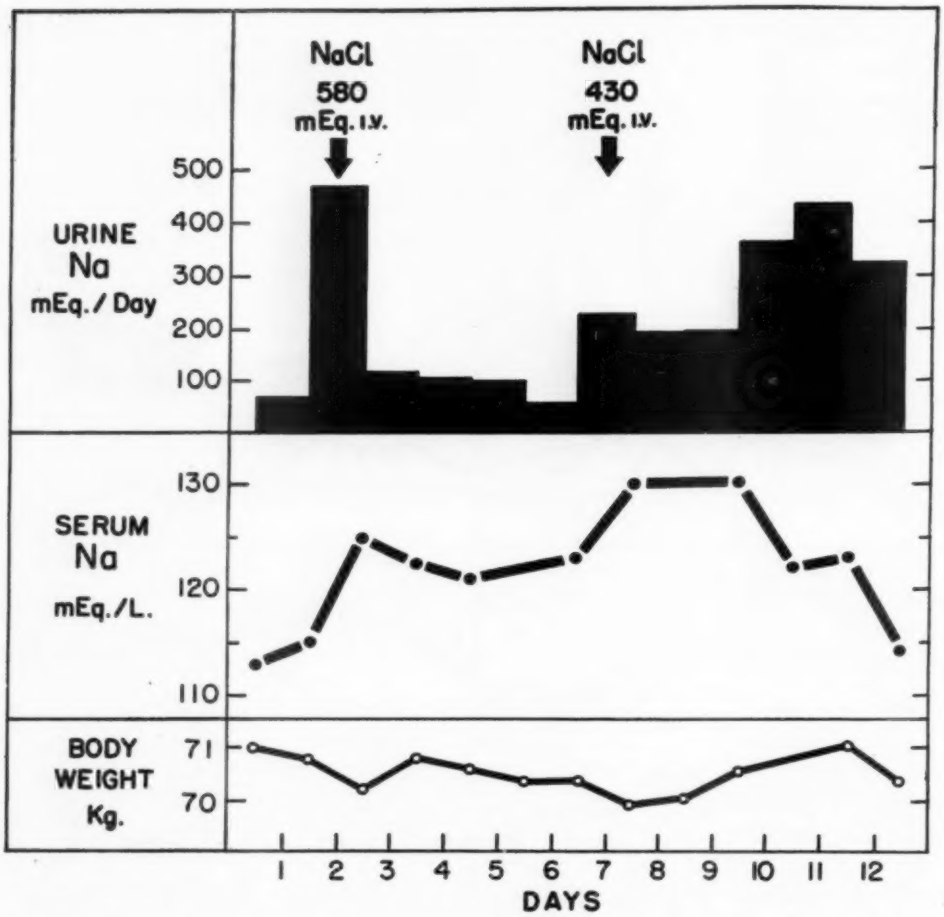

Fig. 2. Urine sodium, serum sodium concentration and body weight during a twelve-day balance study of W. F. Dietary sodium intake was as follows: Days 1 to 7, 80 mEq. Day 8, 180 mEq. Days 9 to 12, 326 mEq.

osmolality between 345 and 537. The body weight at the end of this period was 1.2 kg. less than at the beginning of the period. Loss of 720 cc. by vomitus contributed to this change. The blood urea nitrogen varied between 5 and 9 mg. per cent, the blood pressure remained in the vicinity of 120/70 mm. Hg, and there was no clinical evidence of dehydration. On days 10 and 11, when hyponatremia was most severe, there was nausea, one episode of vomiting, and marked irritability and aggressiveness. Even when the serum sodium concentration was as low as 103 mEq./L., large amounts of sodium were excreted in the urine and no renal sodium conservation was apparent.

When large quantities of sodium chloride were administered intravenously on days 7, 11 and 12, from one-third to one-half of the administered sodium was found in the urine during the days of infusion. The sodium balance was negative by the following day. These loads produced rises in serum sodium concentration of 2 to 11 mEq./L., the highest value attained being 119 mEq./L. There was no increase in body weight with the increases in serum sodium concentration.

Patient W. F. was given sodium chloride intravenously on two occasions while the dietary sodium intake was 80 mEq. per day. (Fig. 2.) On the first occasion, when 580 mEq. were administered, the serum sodium concentration rose from 115 to 125 mEq./L. More than two-thirds of the total sodium intake was found in the urine during the day of infusion, and the sodium balance was negative by the following day. Four days later when the serum sodium concentration was 123 mEq./L., the patient received an infusion of 430 mEq. of sodium chloride. The serum sodium concentration rose to 130 mEq./L. and during this day more than 40 per cent of the total sodium intake was found in the urine. Sodium balance was negative by the following day. During the subsequent four days oral sodium intake was maintained at 326 mEq. per day. The sodium balance became

TABLE I

BALANCE DATA FOR A THIRTY-FIVE DAY STUDY OF PATIENT W. A.

			Intake					Urine									Stool				Serum						
Day	DOCA (mg./24 hr.)	Body Weight (kg.)	Fluid (cc./day)	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	Vol. (cc.)	mOsmolality	Total mOsm./day	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	NH_4 (mEq./day)	Titratable acidity (mEq./day)	Na (mEq./day)	K (mEq./day)	Cl (mEq./day)	N (Gm./day)	pH	CO_2 (mEq./L.)	Na (mEq./L.)	K (mEq./L.)	Cl (mEq./L.)	BUN (mg./100 cc.)	mOsmolality
1	20	66.60	2946	62	100	83	9.0	920	602	554	72	37	127	5.4	63	9.0	7	17	9	10.0	....	....	136	4.1	105	..	282
2	..	67.06	2821	59	95	80	8.3	1200	510	612	86	47	144	6.1	64	9.8	7	17	9	10.0	7.46	27.7	133	3.7	100	8	272
3	..	68.08	2946	62	85	83	8.5	2500	309	773	213	37	185	5.8	38	0	7	17	9	10.0	7.48	28.6	128	3.7	90	8	267
4	..	66.77	2946	59	85	80	8.3	1600	350	560	142	21	101	5.0	23	0	7	17	9	10.0	7.54	27.4	124	3.7	86	..	249
5	..	67.85	2906	59	100	80	8.8	1420	428	608	167	42	109	6.5	12	0	7	17	9	10.0	7.50	25.8	120	4.5	88	7	236
6	..	67.59	2946	59	100	80	8.8	1720	493	848	170	82	147	6.4	14	0	7	17	9	10.0	7.40	22.7	120	4.2	89	8	238
7	..	66.66	3846	608	51	614	4.4	3449	360	1242	393	90	428	8.1	50	11.0	7	17	9	10.0	7.46	24.3	108	4.4	81	8	220
8	..	66.24	2126	30	50	41	4.8	950	537	510	143	36	151	4.7	23	2.3	7	17	9	10.0	7.44	23.0	119	4.5	93	7	248
9	..	66.09	2946	43	83	62	7.3	1318	478	630	160	66	161	5.5	17	0	7	17	9	10.0	7.47	22.6	112	4.8	85	5	235
10*	..	66.36	2495	22	32	28	7.1	2320	363	842	242	69	197	7.4	26	0	7	17	9	10.0	7.47	22.8	113	4.5	80	6	227
11†	..	64.73	1705	0	0	0	0	1095	345	378	86	26	64	3.7	15	0	7	17	9	10.0	7.49	22.4	105	4.4	80	6	220
		65.43	410	357	0	357	0	640	333	213	49	13	39	2.6	17	0	..	..	..	....	....	....	103	...	...	..	202
12	..	64.40	2554	396	20	416	0	2083	401	835	244	42	248	6.7	48	7.3	7	17	9	10.0	7.48	20.9	113	4.1	86	7	230
13	..	63.63	2979	7	32	13	7.1	1765	391	690	162	33	199	6.4	54	5.1	7	17	9	10.0	7.49	21.1	115	4.3	90	9	231
14	..	63.85	3034	359	8	361	1.5	2360	345	814	212	36	230	7.3	59	0	7	17	9	10.0	7.50	22.5	109	4.1	83	8	227
15	20	63.53	2980	360	32	366	7.1	2110	332	701	154	46	233	6.3	67	16.5	7	17	9	10.0	7.49	21.7	115	3.9	87	6	230
16	20	63.34	2943	408	32	413	7.1	2037	350	713	169	43	247	6.3	69	11.4	7	17	9	10.0	7.50	22.8	118	2.8	93	5	250
17	20	63.33	2916	265	84	322	7.1	1560	446	696	131	44	221	7.2	85	15.3	7	17	9	10.0	7.50	24.4	123	3.3	98	6	238
18	20	64.07	2911	278	94	345	7.1	1110	456	506	91	40	153	5.4	44	7.7	7	17	9	10.0	7.51	24.4	124	3.0	99	7	251
19	20	65.00	2982	278	99	350	7.1	875	435	381	68	39	120	4.3	34	7.9	7	17	9	10.0	7.50	24.1	129	3.2	100	8	258
20‡	20	66.55	1558	296	64	333	7.1	1980	415	822	193	86	287	6.9	52	16.4	7	17	9	10.0	7.52	24.9	128	3.1	98	8	255
21	20	63.65	1863	281	67	321	7.1	1510	470	710	161	78	237	6.2	42	17.7	.3	7	3	0.7	7.50	25.5	132	3.1	102	9	268
22	20	63.29	3052	42	72	87	7.1	1030	490	505	84	61	142	5.7	38	17.8	3	7	3	0.7	7.52	26.5	135	3.0	104	9	271
23	20	64.46	2800	42	72	87	7.1	1420	415	589	66	72	131	8.5	47	21.2	3	7	3	0.7	7.51	26.1	130	3.0	100	9	262
24	20	64.96	2325	42	72	87	7.1	2025	278	563	67	77	121	8.0	43	15.2	3	7	3	0.7	7.53	25.7	125	2.7	95	13	258
25	20	64.41	3060	42	76	87	6.4	1900	291	553	61	75	112	8.3	48	14.3	3	7	3	0.7	7.57	26.3	127	2.9	94	12	260
26	20	64.80	3085	42	76	87	6.4	2120	254	538	63	78	115	7.4	53	9.3	3	7	3	0.7	7.49	25.2	127	2.6	96	7	256
27‡	20	64.94	3070	42	76	87	6.4	2042	198	404	44	58	88	5.5	49	9.0	3	7	3	0.7	7.52	26.9	125	2.6	94	10	250
28	5	64.32	3070	42	76	87	6.4	2675	178	476	68	60	108	5.6	54	8.6	3	7	3	0.7	7.51	25.6	121	2.3	94	8	248
29	5	64.15	3070	42	72	87	7.1	3540	167	591	106	55	138	6.0	53	9.6	3	7	3	0.7	7.52	26.2	123	2.6	92	6	247
30	5	63.22	3070	42	72	87	7.1	2475	213	527	96	53	116	5.7	50	7.4	3	7	3	0.7	7.52	26.2	124	2.6	97	6	250
31‡	5	63.13	3070	39	62	83	4.1	1720	311	535	107	67	124	5.2	40	5.8	3	7	3	0.7	7.52	25.5	122	2.8	90	8	248
32	..	63.84	3070	35	61	80	4.1	2615	215	562	108	40	124	4.3	52	6.3	3	7	3	0.7	7.52	23.7	119	2.8	87	8	239
33	..	63.16	3070	42	72	87	7.1	3425	178	610	156	41	151	7.9	39	5.8	3	7	3	0.7	7.53	24.5	120	3.0	86	7	238
34	..	62.06	3070	42	72	87	7.1	2788	195	544	143	37	126	5.0	34	4.5	3	7	3	0.7	7.51	25.0	119	3.4	87	7	240
35	..	61.30	3070	42	72	87	7.1	2410	200	482	134	42	123	4.7	28	4.3	3	7	3	0.7	7.53	21.6	115	3.6	87	6	237
36	..	61.06	....	...	...	...	...	....	...	...	...	..	...	...	..	....	..	..	..	....	7.50	21.3	117	4.1	87	..	240

* Additional volume loss of 720 cc. vomitus, 7.8 mEq. Na, 9.4 mEq. K, 20.6 mEq. Cl, 1.5 gm. N.

† Additional volume loss of 385 cc. vomitus, 8.6 mEq. Na, 5.3 mEq. K, 35.4 mEq. Cl, 0.3 gm. N.

‡ Enema given on this day.

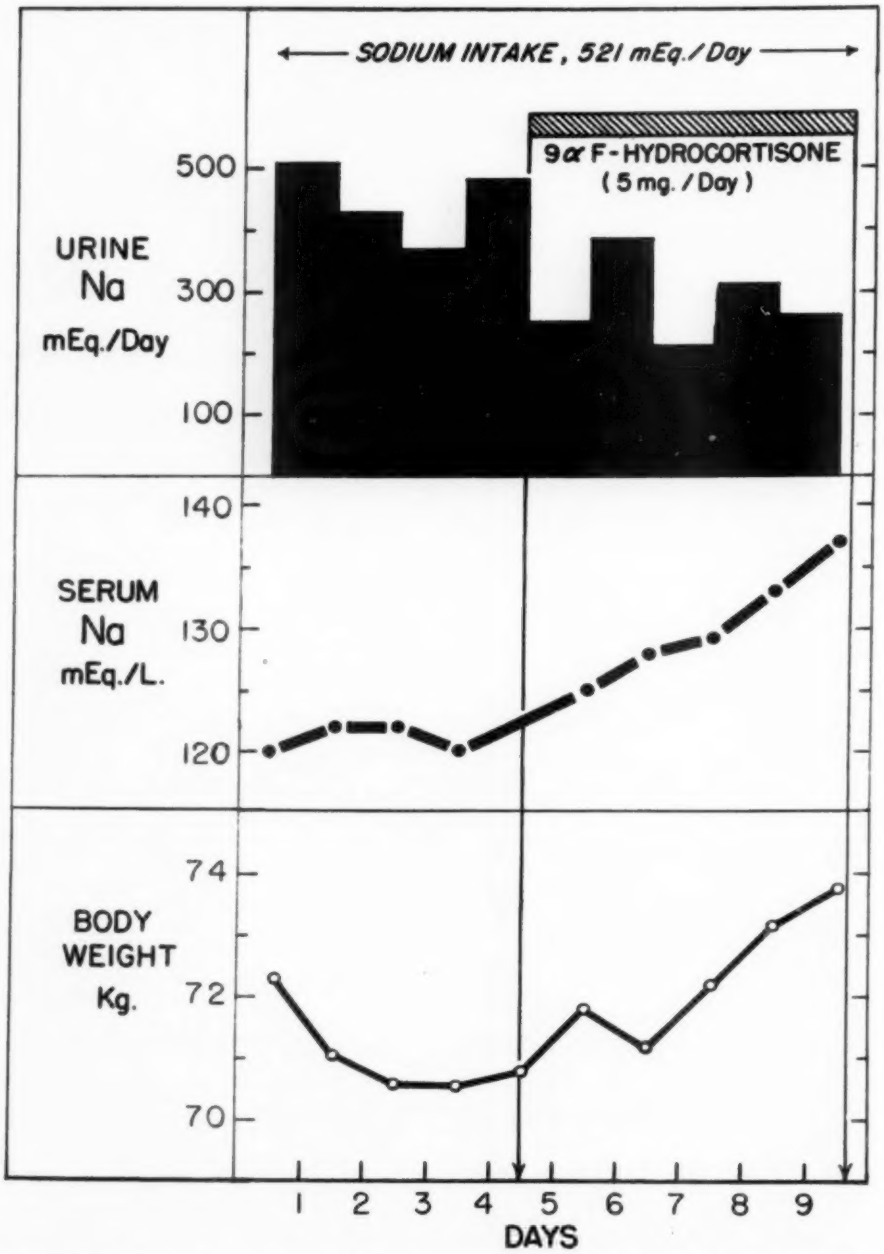

FIG. 3. Urine sodium, serum sodium concentration, body weight and steroid therapy during a nine-day study of W. F.

negative by the second day of this regimen, and the serum sodium fell from 130 to 114 mEq./L. Body weight throughout this entire twelve-day period of study remained essentially unchanged. It should be noted that the values for urinary sodium excretion are minimal figures; the determined sodium balance would have been more negative (or less positive) had there not been instances of urinary incontinence. Simultaneous urine and serum osmolality determined on many occasions consistently showed that the urine was hypertonic to the serum even when the serum osmolality was markedly subnormal. Thus while the plasma osmolality ranged from 240 to 260, the urine osmolality ranged between 390 and 590.

Summary: Both subjects showed continuous urinary sodium loss without corresponding loss of water or body weight. Despite progressive falls of serum sodium and osmolality, the urine remained continuously hypertonic to the plasma. Only transient elevations of serum sodium could be produced with large "loads" of hypertonic saline solution.

Effect of Sodium-Retaining Steroids. DOCA, 20 mg., or fluorohydrocortisone, 5 mg., high sodium intake: DOCA, 20 mg. daily, was administered to W. A. (Table I and Fig. 1) for seven days (days fifteen to twenty-one) while the sodium intake was maintained between 265 and 408 mEq. per day by the administration of additional sodium chloride intravenously, as shown in Figure 1. The urine sodium fell steadily for the first five days to reach a lower limit of 68 mEq. on the fifth day (day 19) and then rose to approximately three times this figure despite the continued administration of DOCA [*2*]. Despite this rise in sodium excretion, sodium balance remained positive throughout the seven-day period with a total positive sodium balance of 1,154 mEq. The urine osmolality ranged between 332 and 470. During this time the serum sodium concentration rose from 115 to 135 mEq./L. and serum osmolality from 230 to 271. The body weight rose during the first five days by a total of 3 kg. and then fell abruptly to the initial level. This weight loss was attributable to removal by enema of a large quantity of feces which had been accumulating throughout the entire study. The serum potassium fell from 4.1 mEq./L. to 2.3 mEq./L. during administration of DOCA, and returned to the initial level after DOCA was stopped. Hydrogen ion excretion, as estimated from urine ammonium and titratable acidity, rose when DOCA was administered, and fell again when it was discontinued.

Fluorohydrocortisone, 5 mg. daily, was administered to W. F. (Fig. 3) after a preliminary four-day period during which his serum sodium concentration had been maintained at levels of approximately 120 mEq./L. by daily administration of 520 mM. of sodium chloride. On this medication the serum sodium concentration rose in stepwise fashion to 137 mEq./L., and the body weight rose by 3 kg. Urine sodium fell to approximately half of the control values, indicating sodium retention of approximately 1,000 mEq. during the treatment. The actual figure may have been somewhat less, because there were small losses of urine, estimated to be less than 5 per cent of the average daily volume. The study was discontinued because of severe hypokalemia.

DOCA, 20 mg., low sodium intake (Table I and Fig. 1): DOCA in a dose of 20 mg. daily was given to patient W. A. for an additional six days (days twenty-two to twenty-seven), with a sodium intake of 42 mEq. daily. The urine sodium fell abruptly with institution of the low sodium regimen but did not become as low as the intake until the sixth day. There was a total negative sodium balance of 151 mEq. during this six-day period. Urine osmolality fell from 490 to 198. During this time the serum sodium concentration fell from 135 mEq./L. to 121 mEq./L. and serum osmolality from 271 to 248. The body weight rose a total of 1 kg. during this six-day period.

DOCA, 5 mg., low sodium intake (Table I and Fig. 1): DOCA, 5 mg. daily, was given to W. A. for four days (days twenty-eight to thirty-one) together with a sodium intake of 42 mEq. per day. The urine sodium rose to approximately 100 mEq. per day. There was a total negative sodium balance of 224 mEq. Urine osmolality ranged from 167 to 311. The serum sodium concentration was 121 mEq./L. at the beginning and 119 mEq./L. at the end of the period. Body weight fell 0.5 kg.

Withdrawal of DOCA (Table I and Fig. 1): DOCA was withdrawn from patient W. A. (Table I, Fig. 1) and the effects observed for a four-day period (days thirty-two to thirty-five) with a dietary sodium of 42 mEq. per day. The urine sodium excretion rose further, and there was a total negative balance of 392 mEq. The urine osmolality ranged from 178 to 215. The serum sodium concentration was 119 mEq./L. at the beginning and 117 mEq./L. at the end of the period. Body weight fell by 2.8 kg.

Summary: Both subjects responded to salt-retaining steroids with normal sodium retention. The serum sodium concentration and body weight rose.

Effect of Changes in Fluid Intake. (Figs. 4, 5 and 6.) Three months after the initial metabolic studies, W. A. (Fig. 4) was admitted to the hospital for study of the effects of dehydration on electrolyte excretion. He was given a daily water intake of approximately 2,000 cc., a value about twice that which he had been taking, and approximately 10 mEq. of sodium. After a three-day control period he was subjected to dehydration for six days and then a liberal intake of fluid was resumed. During the first three days, when the fluid intake was liberal, the patient's urine sodium varied between 75 and 109 mEq. per day, and urine osmolality between 490 and 641. The serum sodium concentration decreased from 127 to 114 mEq./L. Body weight did not change significantly. With dehydration the urine sodium decreased steadily to a minimum value of 6 mEq. per day. During the afternoon and

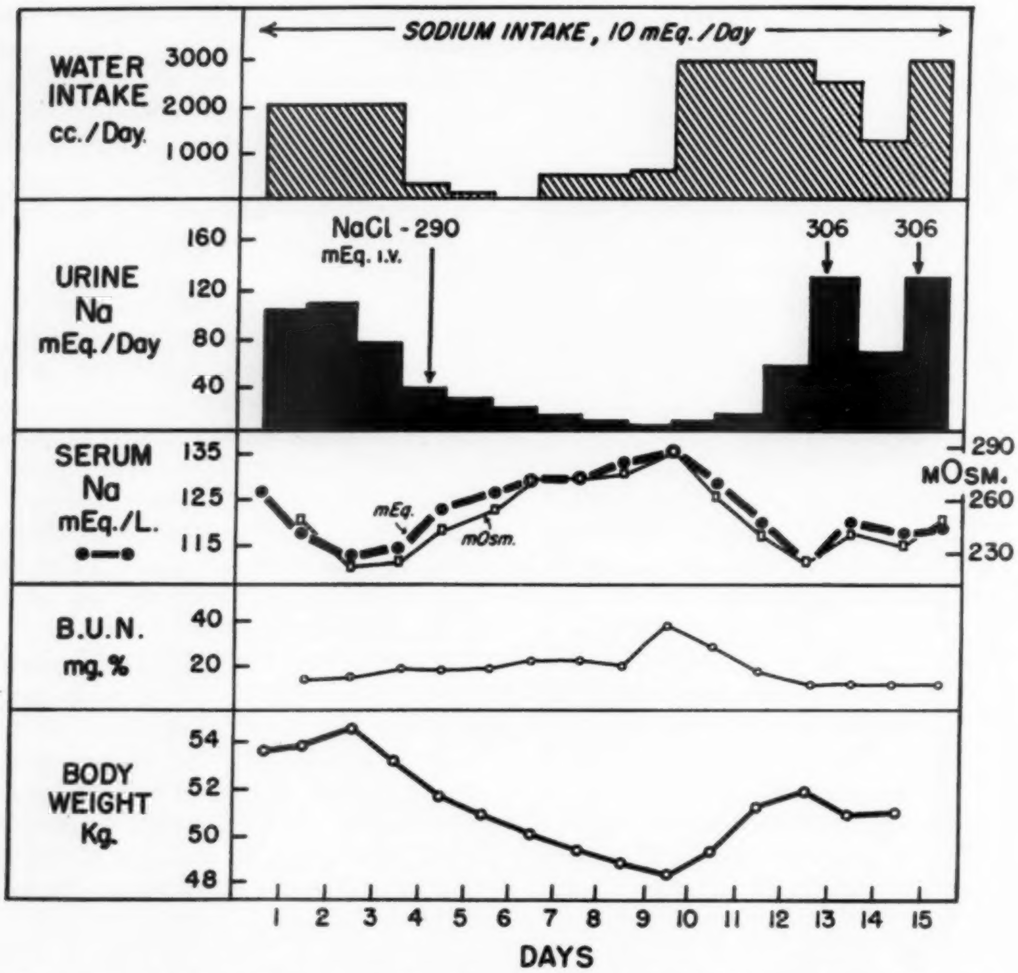

FIG. 4. Fluid intake, urine sodium, blood urea nitrogen, serum sodium and osmolality, and body weight during a fifteen-day study of W. A. Supplementary sodium intake is indicated by arrows.

evening of the first day of dehydration, 290 mEq. of sodium chloride were given intravenously as a 5 per cent solution. In contrast to the very large sodium diuresis produced by similar procedures previously, the sodium excretion fell to 36 mEq. per day. The serum sodium concentration rose from 114 to 123 mEq./L., and during the next five days increased to 135 mEq./L. The body weight fell by 4.9 kg. With rehydration, the urine sodium rose progressively as the serum sodium fell. Body weight rose by 2.6 kg. On the third day 56 mEq. of sodium was excreted on an intake of 10 mEq. When sodium loads were given after rehydration (Fig. 4, days thirteen and fifteen), there were again large increases in urinary sodium. The blood urea nitrogen showed a transitory rise during dehydration.

In W. F. (Fig. 5) after the fluid intake had been 2,000 cc. per day for a two-week period, with maintenance of a normal serum sodium concentration and an essentially constant body weight, the fluid intake was increased to 3,000 cc. per day. There promptly followed a marked rise in urinary sodium excretion to figures greater than the intake (140 mEq. per day), and a fall in serum sodium concentration from 142 mEq./L. to 120 mEq./L., while body weight rose 2 kg.

W. A. was subjected to a rapid expansion of extracellular fluid by the administration of 2,000 cc. of sodium chloride solution intravenously over a two-hour period, at a time when his serum tonicity was subnormal (sodium 116 mEq./L., 234 mOsm.). (Fig. 6.) The concentration of sodium in the infusion was 142 mEq./L. This was sufficient to raise the serum sodium and osmolality by small but significant amounts during the infusion. The procedure resulted in a rise in urine flow from between 1 and 2 cc. to 17 cc. per minute. Urine osmolality fell progressively from 449 to 151 and the osmolar

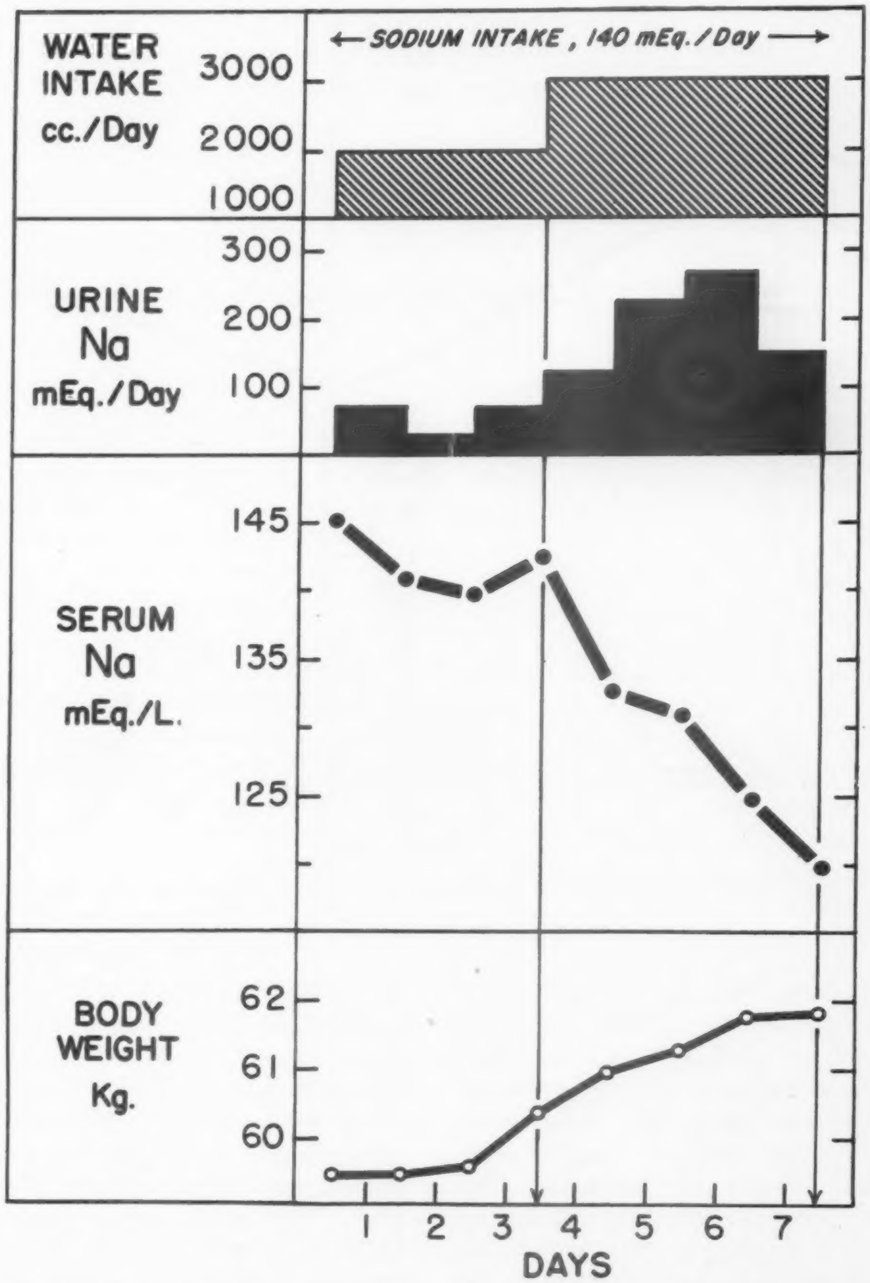

FIG. 5. Fluid intake, urine sodium, serum sodium concentration and body weight during a seven-day study of W. F. Minimum osmolality of urine (based on 2 × [Na] + [K]) ranged from 280 to 440 on days 4 through 7.

U/P ratio from 1.75 to 0.60. Concomitantly the sodium excretion rose from initial values of approximately 100 μEq./minute to 1,000 μEq./minute at the height of the diuresis.

Summary: In both subjects fluid restriction led to sodium retention and a return of the serum sodium concentration to normal. Restoration of liberal fluid intake re-established the sodium-losing syndrome. One subject was given a rapid infusion of saline hypertonic to his plasma; this was followed promptly by a reduction in urine osmolality to values below those of the plasma, with copious diuresis.

"Space" Estimations. Radiosulfate, radiosodium and radiopotassium spaces: On day nine (Fig. 1), when the serum sodium concentration was 112 mEq./L., radiosulfate, radiosodium and radiopotassium spaces were determined in W. A. The twenty-minute radiosulfate and radiosodium spaces were 17.2 and 17.3 L. respec-

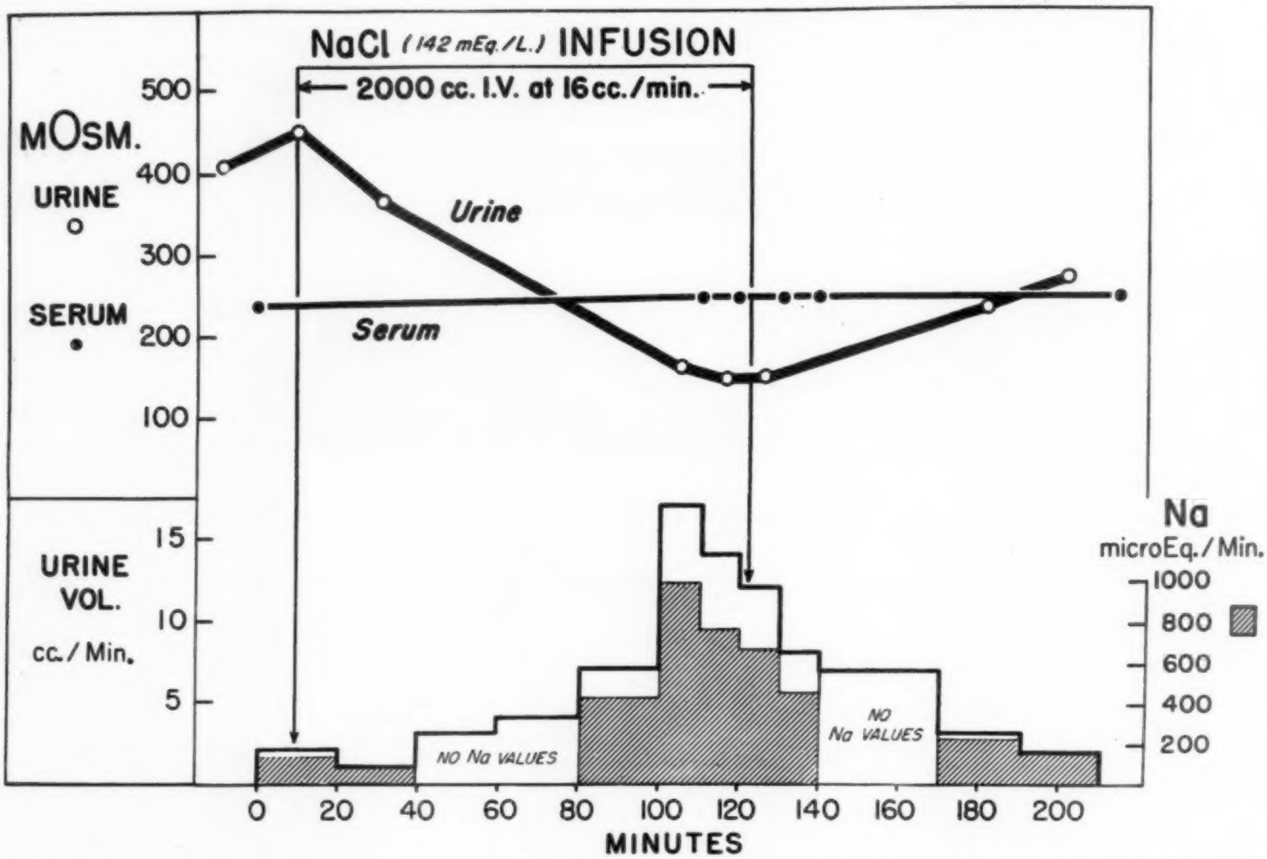

FIG. 6. Urine and serum osmolality, urine volume and urine sodium excretion during the rapid infusion of "normal" saline solution to W. A.

tively, a volume of distribution equal to about 26 per cent of body weight. These values are approximately 50 per cent greater than those obtained in normal subjects by these methods [6,7]. At twenty-four hours the "total body sodium" exchangeable with the isotope was estimated at 2,388 mEq. or 36.3 mEq./kg. This value is approximately 25 per cent below that obtained in normal subjects by this method. If, however, the sodium which had been lost by the patient during the time his serum sodium was falling from normal levels be added to it, then the "corrected" total body sodium is normal (44.8 mEq./kg.). At twenty-four hours the "total body potassium" exchangeable with the isotope was estimated at 2,193 mEq. or 33.3 mEq./Kg. This value is approximately 25 per cent below that obtained in normal subjects by this method. Even when the apparent expansion of extracellular fluid volume is taken into consideration, the corrected per kg. value remains below normal.

"Chloride space" changes: From the data in Table I, chloride spaces were calculated for W. A. They showed (1) a net decrease of 0.3 L. during metabolic days 1 through 6 (Fig. 1) before administration of any salt loads, (2) a net decrease of 0.4 L. during metabolic days 1 through 9, which included a salt load on day 7, (3) an increase of 5.7 L. during metabolic days 15 through 21 when DOCA was administered with a high salt intake, (4) a decrease of 0.2 L. during metabolic days 22 through 31 when DOCA was given with a low salt intake, and (5) a decrease of 2.3 L. during metabolic days 32 through 35 after DOCA was discontinued.

Summary: The extracellular fluid volume appeared to be substantially above normal in the one subject in whom it was estimated. In this subject, chloride space did not decrease significantly as hyponatremia developed but increased markedly during administration of DOCA.

Adrenal Function. The clinical findings relevant to adrenal function were as follows: There was no abnormal pigmentation, axillary and pubic hair were normal, and blood pressure was normal in one subject and persistently high in the other. Even with severe hyponatremia, there was no evidence of dehydration, blood pressure remained unchanged, and there was no fever, diarrhea or rise in serum potassium con-

centration. In both patients (*vide supra*) a normal serum sodium concentration could be maintained for extended periods by simple fluid restriction with low or moderate sodium intake.

In W. A., circulating eosinophils fell from 700 to 187 after eight hours of administration of ACTH; twenty-four-hour urinary 17-hydroxycorticoids rose from 6.4 to 12.7 mg. Aldosterone excretion was measured twice on low and twice on high sodium intakes while the serum sodium concentration ranged from 103 to 115 mEq./L., and showed a range from 3 to 5 μg. per day. In W. F., circulating eosinophils fell from 188 to 13 after eight hours of administration of ACTH; plasma 17-hydroxycorticoids rose from 8 to 35 μg. per 100 cc., and twenty-four-hour urinary 17-hydroxycorticoids rose from 9 to 22 mg. Aldosterone excretion was measured on a normal sodium intake (80 mEq. per day), while the serum sodium concentration was 120 mEq./L., and was found to be 5 μg. per day.

The pathologic findings (*vide supra*) showed normal adrenal cortices in the subject who died shortly after the studies were completed, and extensive invasion of the adrenal cortices in the other who died eight months after the studies were made.

Summary: Both subjects showed normal adrenal cortical function as judged from clinical and biochemical evidence.

Renal Function. The urine was normal on numerous occasions in both subjects, as was the blood urea nitrogen. In W. A. the inulin clearance was 120 cc./minute and the p-aminohippurate clearance 694 cc./minute, when the serum sodium concentration was 108 mEq./L. In W. F. the inulin clearance was 170 cc./minute and the p-aminohippurate clearance 650 cc./minute, when the serum sodium concentration was 124 mEq./L.

The pathologic findings (*vide supra*) showed that the kidneys were normal both grossly and microscopically except for scattered metastases in one subject and minor arteriosclerotic changes in both.

Summary: Both subjects showed normal renal function as judged from urinalyses, glomerular filtration rates and renal plasma flows.

COMMENTS

These two patients with mediastinal tumors presented a syndrome in which the cardinal feature was hyponatremia. Renal and adrenal cortical function was normal. As hyponatremia and hypotonicity of the extracellular fluid developed, the urine was persistently hypertonic to the plasma. According to current concepts, hypertonicity of the urine, in the presence of a normal glomerular filtration rate, constitutes *prima facie* evidence for the presence of antidiuretic hormone (ADH) [*8–10*]. It is postulated that there was sustained, inappropriate secretion of ADH in these subjects, and that this was responsible for the disorder of sodium metabolism. When pitressin and abundant fluids are given continuously to normal subjects a similar pattern of hyponatremia with persistently concentrated urine also is observed [*11*]. Normal subjects treated in this fashion* exhibit negative sodium balance, as did the patients in the present study [*11*]. When, on the other hand, pitressin is given continuously to normal subjects and fluid intake is restricted, hyponatremia and urinary sodium loss do not occur; similarly, sodium loss ceased and serum sodium concentration rose to normal values when the patients' fluid intake was restricted.

The production of ADH in these subjects could not have been governed by normal osmoregulatory mechanisms [*13*], since it persisted in the face of progressive reduction in the tonicity of the plasma. Reduction of extracellular fluid volume may lead to elaboration of an hypertonic urine, possibly via the secretion of ADH [*14*]. There was no clinical evidence of dehydration in the subjects reported here. Indeed, the values for the twenty-minute radiosulfate and radiosodium spaces indicated that the extracellular fluid volume in W. A. was increased at a time when the serum sodium concentration was far below normal. In the absence of any known stimulus to ADH production, it appears likely that its continued inappropriate secretion was a result of the disease process.

It is unlikely that the continued production of ADH in these subjects represented a lowered threshold for stimulation of osmoreceptors (such as might result from primary reduction of the osmolality of cells), since hypertonicity of the urine persisted in spite of a plasma osmolality as low as 202. The response to sodium-retaining steroids furnishes further evidence that the hypotonicity was probably not a result of a very low "setting" of an osmoregulator controlling

* Normal subjects given pitressin while unaware of the nature of the medication and offered water *ad libitum* continued to drink water in sufficient quantities to develop and maintain a severe sodium-wasting syndrome with progressive hyponatremia for as long as two weeks [*12*].

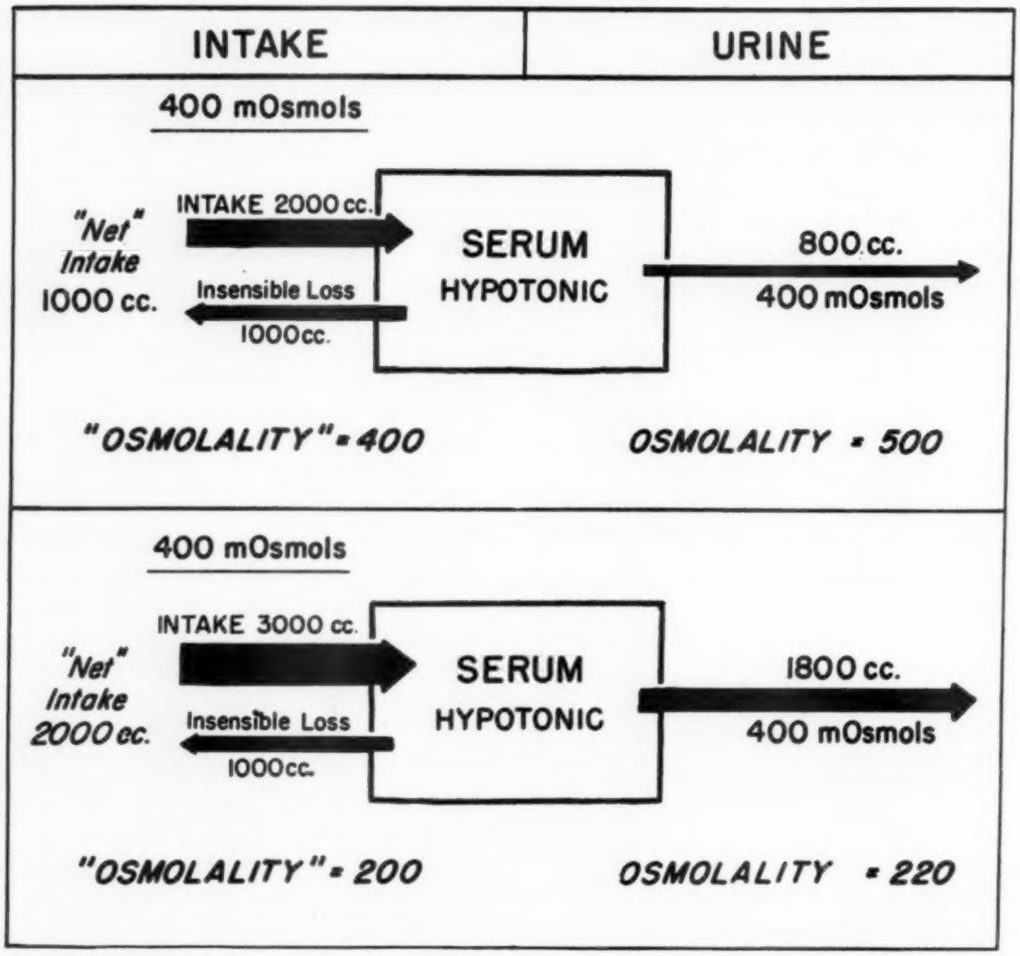

FIG. 7. Diagram to illustrate the production of serum hypotonicity despite urine osmolality below that of plasma. Both subjects are shown as accumulating 200 cc. per day.

the secretion of ADH. If this were the case the sodium retained on steroid therapy should, by producing hypertonicity of body fluid relative to this setting, lead to further output of ADH and further water retention, thus maintaining the hypotonic state. In these subjects, however, serum tonicity rose markedly with steroid therapy, and the urine did not even approach its maximum osmolar concentration.

It should be noted that it is not necessary that the urine be hypertonic to the plasma in order that the tonicity of the serum fall below normal or be maintained at subnormal levels; it is essential only that the "osmolality of the total intake" be lower than or equal to that of the urine.* (Fig. 7.) Indeed, all available evidence indicates that when the urine is not maximally dilute, this alone, in the presence of a normal glomerular filtration rate, constitutes evidence for the continued presence of ADH.

When W. A. was subjected to a rapid expansion of his extracellular fluid with saline slightly hypertonic to his serum, there ensued a copious diuresis of hypotonic urine (17 cc./minute with osmolar U/P .61). A response such as this to expansion of body fluid volume may explain the failure of these subjects to retain water indefinitely. It is likely that a critical expansion of volume would be reached spontaneously which would set in operation a similar train of events. It is not certain from the evidence at hand whether this phenomenon is the result of a decrease in the production of ADH or represents an "escape" from ADH such as that described in normal subjects given mannitol during constant infusions of pitressin [*15*].

During days 1 through 6 of the metabolic study in W. A. there was no weight change and the serum osmolality fell by 62. If it is assumed that osmotic equilibrium is maintained between

* The "osmolality of the total intake" is here taken to mean the osmolality of an hypothetic solution in which all the actual and potential solute particles in the diet destined for urinary excretion are dissolved in an amount of fluid equal to that in the diet (including water of oxidation) minus that of the "insensible loss."

intracellular and extracellular fluid, and that total body water is not less than 50 per cent of the body by weight, this implies the removal of approximately 2,000 mOsmol. during the six-day period. In fact, there was a slightly positive potassium balance during this period and the negative sodium and chloride balance accounted for only about 1,000 mOsmol. The hazards inherent in the rigid interpretation of cumulative metabolic data are well recognized, but this "osmotic" discrepancy appears to be significant even after liberal allowances are made for skin loss. A similar calculation for the period ending on day 11 gives comparable results. It follows, therefore, if our assumptions are correct, that progressively larger amounts of intracellular solute must have become osmotically "inactive" as the serum tonicity decreased. Whether this was a result or could possibly have been a cause of the inappropriate secretion of ADH postulated here cannot be determined from the information at hand.

During the first six days the fall in serum osmolality would have been expected to result in a gain of approximately 9 L. of intracellular water. However, as there was no increase in body weight, intracellular dilution could not have resulted from a positive water balance. There was no clinical or laboratory evidence that significant amounts of fluid had shifted from the extracellular to the intracellular space. The chloride space did not change, and the radiosodium and radiosulfate determinations showed an abnormally large extracellular volume. The blood pressure did not fall, there were no symptoms suggestive of vascular collapse, and the glomerular filtration rate was normal. One is therefore forced to the conclusion that, as suggested, intracellular solute had become osmotically "inactive."

Weight gain did not occur in either subject when the serum sodium concentration was raised with hypertonic saline solution. When, in contrast, the serum sodium concentration rose as the result of increased tubular reabsorption of sodium produced by steroids, body weight increased and the urine volume decreased. It is unlikely that the water retention with the steroids can be attributed to increased secretion of ADH in response to the rise in serum osmolality [*13*], as in that case it should have occurred with hypertonic saline solution as well. Furthermore, the ADH output in these patients appeared in all other respects to be independent of serum tonicity. If the action of ADH is to allow a dilute tubular urine to become isotonic with plasma at a distal site [*10,16*], then a steroid-induced increase of sodium reabsorption proximally thereto might be expected to allow it to induce more water reabsorption.

After the serum sodium had been raised by infusion of hypertonic saline solution, weight loss did not occur in either subject during the subsequent spontaneous fall in the serum sodium concentration. When steroid therapy was discontinued, however, loss of weight accompanied the sodium loss. The tonicity of the urine fell. This phenomenon may be in part a reversal of the one discussed. It is likely, however, that it represents also a response to overexpansion of the extracellular fluid, exactly analogous to that produced when W. A. was given an infusion of sodium chloride. (Fig. 6.) It should be noted (Fig. 1) that the loss of sodium and water began even before DOCA was discontinued, at a time when the chloride space showed an expansion of 5.7 L. A similar escape from the influence of DOCA has been described for normal subjects [*2*].

These studies do not explain the mechanism whereby continued inappropriate secretion of ADH might have been produced in these patients. Each patient had a mediastinal tumor, and it may be that the stimulus arose as a result of a direct effect on some intrathoracic structure, such as the vagus nerves [*17*]. Each patient also had brain disease, and this may have served in some fashion to produce continued secretion of ADH. The mechanism by which inappropriate ADH in turn allows sodium loss probably involves (1) an increase of glomerular filtration rate [*3*] and (2) a failure of aldosterone secretion to rise as it would from the volume contraction which ordinarily accompanies sodium depletion [*3*].

Asymptomatic hyponatremia with appreciable sodium in the urine has been reported in patients with pulmonary tuberculosis and meningitis [*18–21*] and in one patient with bronchogenic carcinoma [*18*]. These patients resembled those reported here in showing no dehydration, vascular collapse or nitrogen retention as the serum sodium fell. In fact, normal to high extracellular fluid volumes have been observed in patients with hyponatremia and tuberculous meningitis [*21,22*]. Patients with so-called asymptomatic hyponatremia previously reported on differ from our subjects in that their serum sodium concentration tended to stabilize at moderately reduced levels. It is possible that

the mechanism whereby hyponatremia was produced and maintained in some of the reported cases was related to that in our two patients, but critical data bearing on this point are not available.

SUMMARY AND CONCLUSIONS

Studies are reported on two subjects with bronchogenic carcinoma who had marked progressive hyponatremia with urinary sodium loss, despite normal renal and adrenal function. The urine was persistently hypertonic to the plasma, and contraction of body fluid volume did not occur as sodium depletion and hypotonicity of the plasma progressed.

It is postulated that the underlying disease process induced in some manner a sustained, inappropriate secretion of antidiuretic hormone, and that the syndrome was a consequence of the resultant expansion of body fluid volume.

All the essential features have been produced in normal subjects by continuous administration of pitressin and water. As with the normal subjects, restriction of fluids in the patients reported here prevented sodium loss and hyponatremia.

It is possible that the hyponatremia previously reported in patients with pulmonary and central nervous disease has a similar pathologic physiology, but critical data to settle this question are not available.

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Hypernatremia, Azotemia and Acidosis after Cerebral Injury*

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In recent years, attention has been focused on the incidence of hypernatremia and/or hyperchloremia in patients who have disorders of the central nervous system [*1–19*]. Examination of these patients also has revealed the presence of hyponatruria and/or hypochloruria [*1–4,7–11,13,14,17–19*], azotemia [*1–4,6,7,10–13, 17,18*], and frequently hypokalemia or hyperkaluria [*1,3,6,9,10,12,15,18*]. Frank renal lesions were present in only two series [*2,3*]. Neurohypophyseal insufficiency was present in only four cases [*14–16,19*]. In view of these facts, some investigators have proposed a causal relationship between the disturbance of the central nervous system and hypernatremia.

This report concerns two patients in whom hypernatremia, azotemia and acidosis developed following severe craniocerebral trauma, with abnormalities in the serum potassium concentrations and the electrocardiograms. Possible mechanisms are discussed and the pertinent literature reviewed. Therapeutic implications are noted.

CASE REPORTS

CASE I. A white man, thirty-four years of age, who had been hit by a truck, was unconscious when admitted to the Neurosurgical Service of Brooke Army Hospital on January 20, 1952. Examination revealed lacerations, abrasions and contusions of the lower extremities. The blood pressure was 125/80 mm. Hg; pulse rate, 120; respiratory rate, 36; and the temperature, 104°F. Localizing neurologic signs were not present. During the evening of the first day blood pressure increased to 170/110 mm. Hg, pulse rate to 168, and respiratory rate to 48. The coma deepened, and there was marked decerebrate rigidity and a 2 plus papilledema. Bilateral trephines in the temporal and parietal regions revealed a tense, non-pulsatile "wet" brain with 30 cc. of clear fluid in the subarachnoid space of the left parietal area. A tracheotomy was performed and an indwelling catheter was inserted into the bladder.

During the first ten days of hospitalization the patient remained unconscious and could not be aroused. His temperature ranged from 101° to 105°F. but was usually between 102° and 104°F. Tachypnea, ranging from 24 to 48 respirations per minute, with shallow to normal respiratory excursion and constant profuse diaphoresis were evident. Except for episodes of tachycardia and hypotension on January 23 and 28, for which albumin was administered intravenously the pulse rate and blood pressure remained moderately elevated. During this ten day period the patient received an average daily intake of 45 gm. of protein, 35 mEq. of potassium, 21 mEq. of sodium and 2,460 cc. of water. The average daily urinary volume was 1,020 cc. The specific gravity of the urine was recorded as 1.022 on January 28. The blood urea nitrogen was 49 mg. per 100 cc. on January 24 and 112 mg. per 100 cc. on January 29; additional blood chemistry studies were not performed.

In Figures 1A and B, some pertinent findings from the eleventh through the fortieth hospital days are shown. On February 1, twelve days after the patient's admission to the hospital, the blood urea nitrogen was 154 mg. per 100 cc. and the plasma bicarbonate was 21 mEq./L. Later that day the blood pressure decreased to 90/70 mm. Hg, the pulse rate increased to 120 and albumin was given intravenously. On February 2 the patient appeared very dehydrated but profuse diaphoresis continued. On February 3 the blood pressure and pulse rate were unobtainable and the patient appeared moribund. Albumin and neosynephrine® were administered intravenously. Plasma electrolyte concentrations at 8:00 A.M. on February 4 were: 192 mEq. of sodium, 8.7 mEq. of potassium, 12 mEq. of bicarbonate and 133 mEq. of chloride per liter. The blood urea nitrogen was 290 mg., the plasma inorganic phosphorus was 12.5 mg. and the total proteins were 8.0 gm. per 100 cc. By 4:30 P.M. the patient received 3,000 cc. of fluid (including neosynephrine, given intravenously, which maintained the blood pressure at 100/80 mm. Hg), but the urinary output was negligible; the plasma concentrations of sodium and potassium had decreased to 170 and 6.2 mEq./L., respectively. An electrocardiogram taken at this time revealed slight T wave changes

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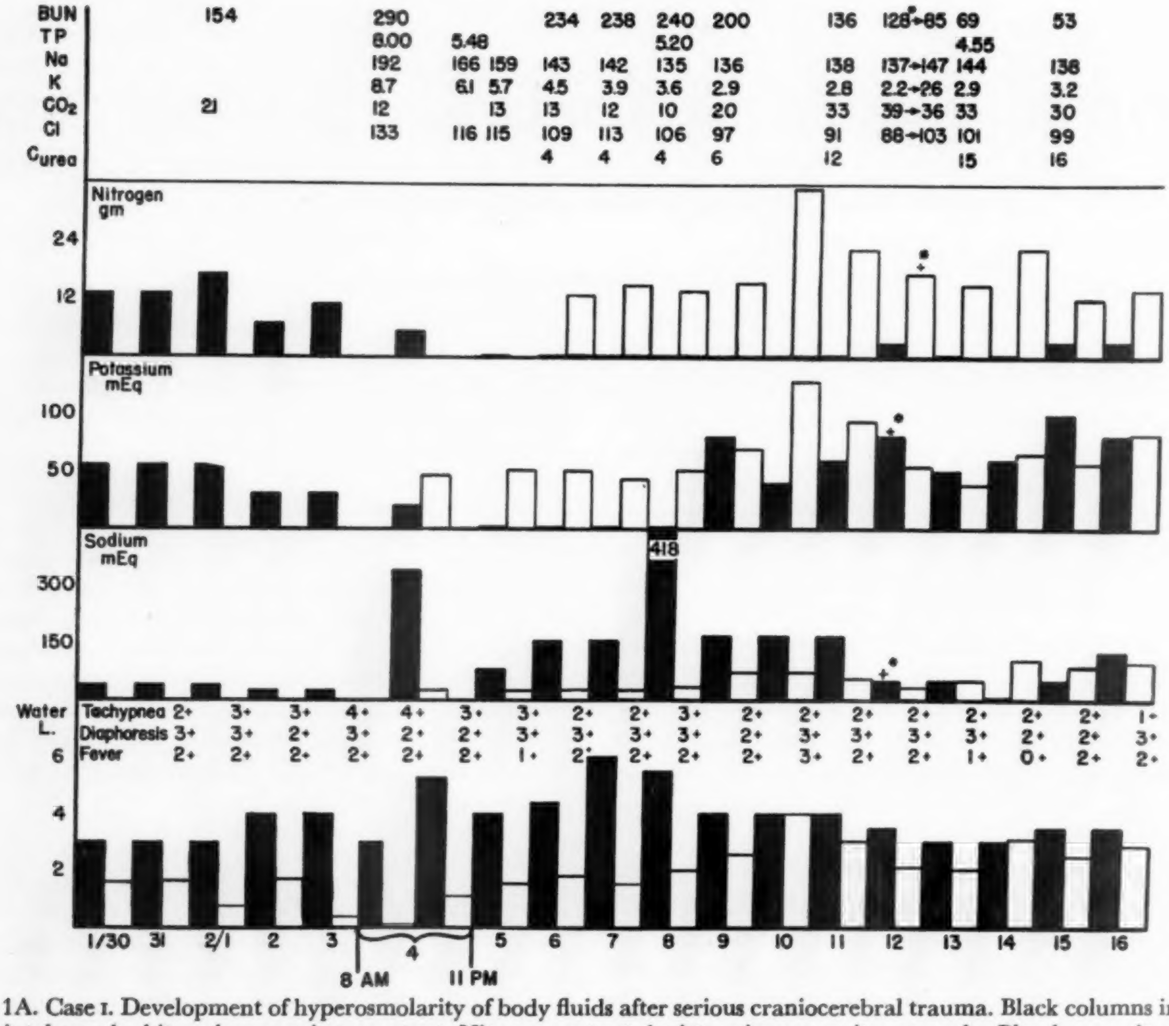

FIG. 1A. Case I. Development of hyperosmolarity of body fluids after serious craniocerebral trauma. Black columns indicate intake and white columns urinary output. Nitrogen output depicts urine urea nitrogen only. Blood urea nitrogen (BUN) is expressed in mg./100 cc., total protein (TP) in gm./100 cc., electrolytes in mEq./L. Urea clearance (C_{urea}) is a twenty-four hour clearance expressed in cc./minute.

* Changes brought about by four hours of extracorporeal hemodialysis with the artificial kidney. Tachypnea, fever and diaphoresis are approximated as follows: Tachypnea: 1 plus, twenty to twenty-four/minute; 2 plus to 28/minute; 3 plus to 32/minute; 4 plus above 32/minute. Fever: 1 plus to 100°F.; 2 plus to 102°F.; 3 plus to 104°F.; and 4 plus above 104°F. Diaphoresis approximated clinically from 1 plus to 4 plus; 4 plus represents continuous drenching perspiration which required at least six bedding changes daily.

compatible with hyperkalemia. (Fig. 2.) During the next twelve hours the patient received 5,240 cc. of water and by 11:00 P.M. the plasma electrolyte concentrations had fallen as shown in Figure 1A. During the twenty-four hours of February 4 the patient received a total of 8,240 cc. of water and 340 mEq. of sodium; the urinary volume was 1,160 cc.; and despite the unusually high concentration of sodium in the plasma, the concentration of this ion in the urine was only 21 mEq./L. The urine specific gravity was 1.008.

From February 5 through February 8 the patient received an average daily intake of 4,975 cc. of water, 200 mEq. of sodium and no potassium or nitrogen. Half of this 800 mEq. of sodium was given as 2,500 cc. of sixth-molar sodium lactate on February 8 because of a laboratory error in the plasma sodium report and because of the decreasing plasma bicarbonate. During this period the volume of urine increased; the urinary sodium concentration averaged only 14 mEq./L.; the urinary nitrogen and potassium excretions were sizable (Fig. 1A), and the plasma concentrations of sodium, potassium, chloride, urea nitrogen and total proteins all decreased. The twenty-four-hour urea clearance was 4 cc./minute and the urinary specific gravity on February 8 was 1.022. Clinically, the dehydration, tachypnea and fever diminished somewhat during this period, but the blood pressure varied from 140/80 to 170/90 mm. Hg. There were short generalized seizures on February 7, 8 and 9. An electrocardiogram taken on February 7 was normal.

From February 9 through February 11 the potas-

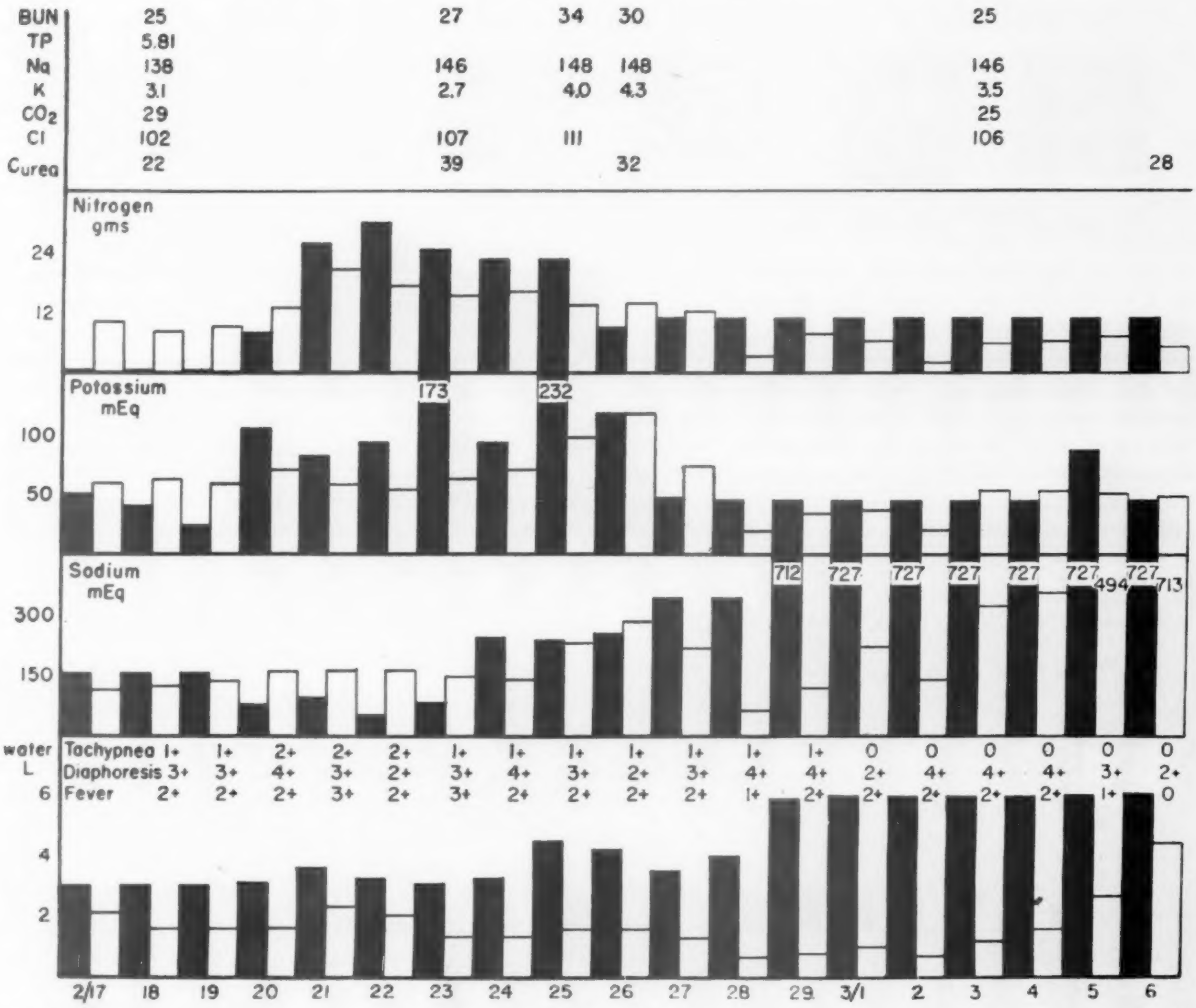

FIG. 1B. Case I. Development of hyperosmolarity of body fluids after serious craniocerebral trauma. Black columns indicate intake and white columns urinary output. Nitrogen output depicts urine urea nitrogen only. Blood urea nitrogen (BUN) is expressed in mg./100 cc., total protein (TP) in gm./100 cc., electrolytes in mEq./L., Urea clearance (C_{urea}) is a twenty-four-hour clearance expressed in cc./minute.

sium intake totaled 181 mEq. and the urinary output 291 mEq.; the nitrogen intake was 0 and the urinary urea nitrogen output was 74 gm. Cheyne-Stokes respirations and cardiac trigeminy were noted on February 11. On February 12 the plasma potassium concentration was 2.2 mEq./L. and there was severe hypochloremic alkalosis and persistant azotemia. (Fig. 1A.) Because it was believed that continued azotemia might be delaying recovery, the patient was given four hours of extracorporeal hemodialysis with the Kolff Brigham artificial kidney [*32*] on February 12 with the resultant changes in the blood shown in Figure 1A. The phenolsulfonphthalein excretion was 56 per cent in two hours on February 13.

The subsequent course of the patient was one of gradual clinical improvement. There was an increase in the level of awareness and a decrease in the pulse rate to normal. The blood pressure remained at approximately 160/110 mm. Hg. By February 18 the patient was able to follow objects with his eyes. By this date the blood urea nitrogen concentration was 25 mg./100 cc., the twenty-four-hour urea clearance was 22 cc./minute and the urinary specific gravity was 1.010. On February 19 further generalized seizures occurred.

On February 20 feeding by tube was instituted and the patient was given an average of 132 gm. of protein daily for five days. The blood urea nitrogen increased on February 25 to 34 mg./100 cc. Evidence of a water deficit was discernible in the increasing plasma sodium concentration (despite negative sodium balance during this period) and the decreasing urinary volumes. Hypokalemia on February 23 was probably the result of antecedent diarrhea.

The profuse diaphoresis was far in excess of the patient's low grade fever and, on occasion, eight to

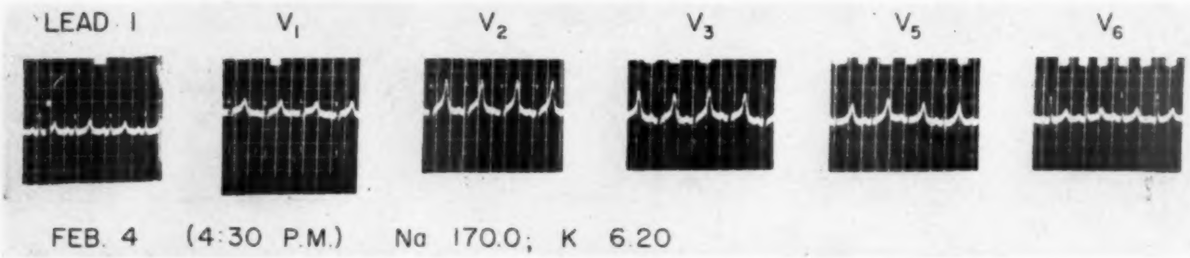

FIG. 2. Case I, Minimal electrocardiographic changes suggestive of slight hyperkalemia. Note the narrow, peaked T waves.

twelve changes of drenched bedclothes were necessary per day. Despite the large intake of fluid, the patient's urinary output decreased to 600 cc. on February 28 and his skin turgor was poor. During the next five days the average daily fluid intake was 6,000 cc. and the average daily urinary volume was 1,025 cc. (Fig. 1B.) It was estimated that he was losing more than 4 L. of fluid daily through his skin. Skin turgor did not become normal until March 5.

During this period the patient became more alert and by March 1 he responded to simple commands and was able to move his extremities. By March 7 he attempted to speak and by the middle of March he was able to answer questions intelligibly. The blood urea

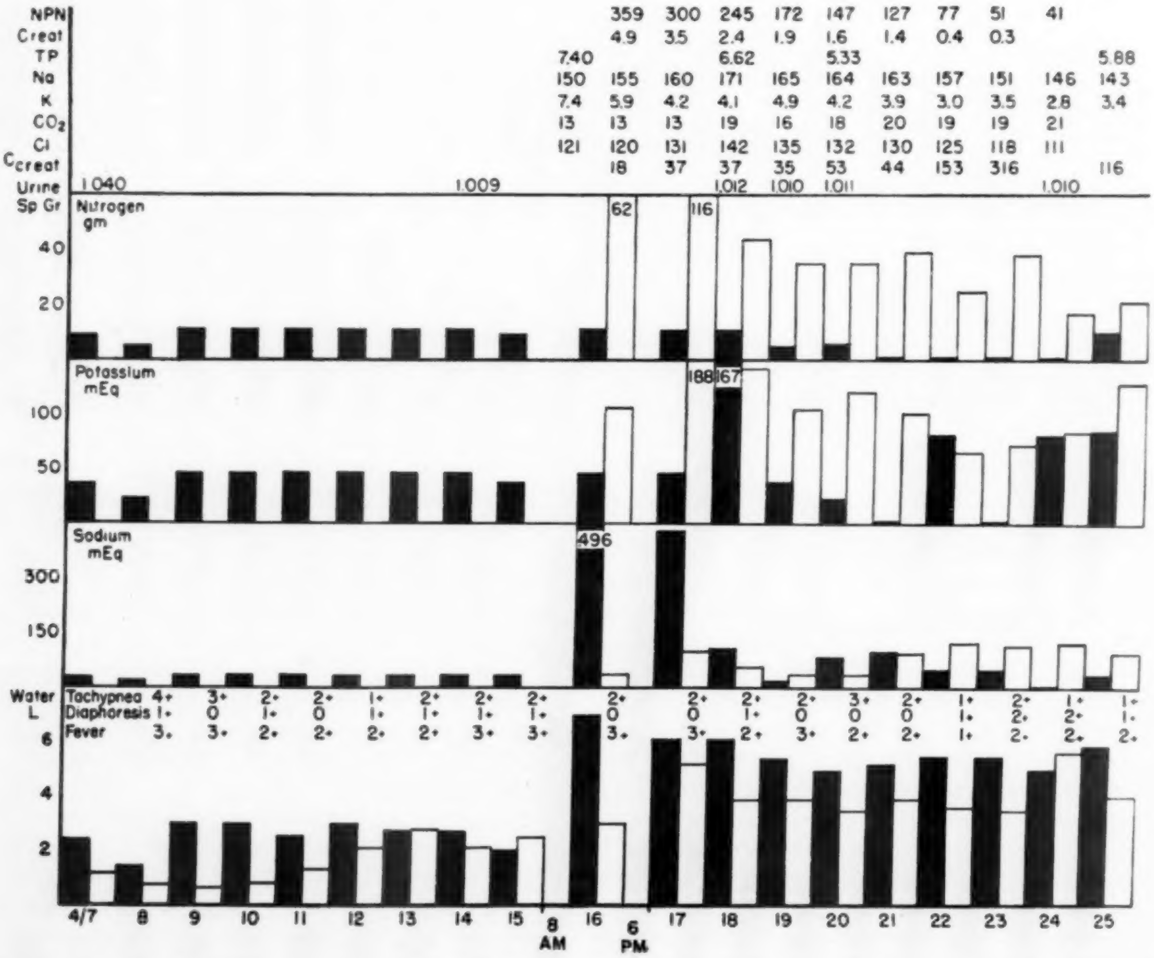

FIG. 3A. Case II. Development of hyperosmolarity of body fluids after serious craniocerebral trauma. Black columns indicate intake and white columns urinary output. Nitrogen output depicts urinary urea nitrogen only. Non-protein nitrogen (NPN) and creatinine (creat.) are expressed in mg./100 cc. Creatinine clearance ($C_{creat.}$) is a twenty-four hour endogenous creatinine clearance expressed in cc./minute. Total protein (TP), electrolytes, tachypnea, diaphoresis and fever are expressed as in Figure 1. Urine specific gravity is measured from the total twenty-four-hour specimens. Urinary chloride excretion tends to follow the same pattern as the urinary sodium excretion.

nitrogen was 14 mg./100 cc. on March 10. Oral feedings were started on March 17; the patient's appetite was voracious. He became afebrile at this time. Both the diaphoresis and hypertension (150/108 mm. Hg) believed to originate in the central nervous system subsided spontaneously by late March. The urinary intake and output were good. On April 8 the urinary specific gravity was 1.025.

The patient's spastic and atrophic muscular residuals have responded to physical therapy and he now ambulates well. His ability to cerebrate is somewhat abnormal. Extreme emotional lability and motor aphasia were present from April to July, 1952, but are no longer evident.

Case II. A white boy, sixteen years of age, was transferred while unconscious from a civilian hospital to the Neurosurgical Service of Brooke Army Hospital on April 7, 1952, ten hours after he suffered a cerebral contusion in an auto collision. An immediate tracheotomy was performed for respiratory obstruction. On admission, the temperature was 105°F.; respiratory rate, 34; blood pressure, 140/100 mm. Hg; and pulse rate, 130. There were lacerations and a hematoma on the right side of the face, slow conjugate nystagmus to the right and right hemiparesis. Babinski's sign was positive bilaterally but papilledema was not evident. Extreme dehydration was present. There were 6.5 million red blood cells per cu. mm. and 20.5 gm. of hemoglobin per 100 cc. The urinary specific gravity was said to be 1.040 with sugar absent. An indwelling catheter was inserted.

Pertinent data from the first thirty-nine days of hospitalization are illustrated in Figures 3A and B. During the first nine days of hospitalization the patient received an average daily intake of 60 gm. of protein,

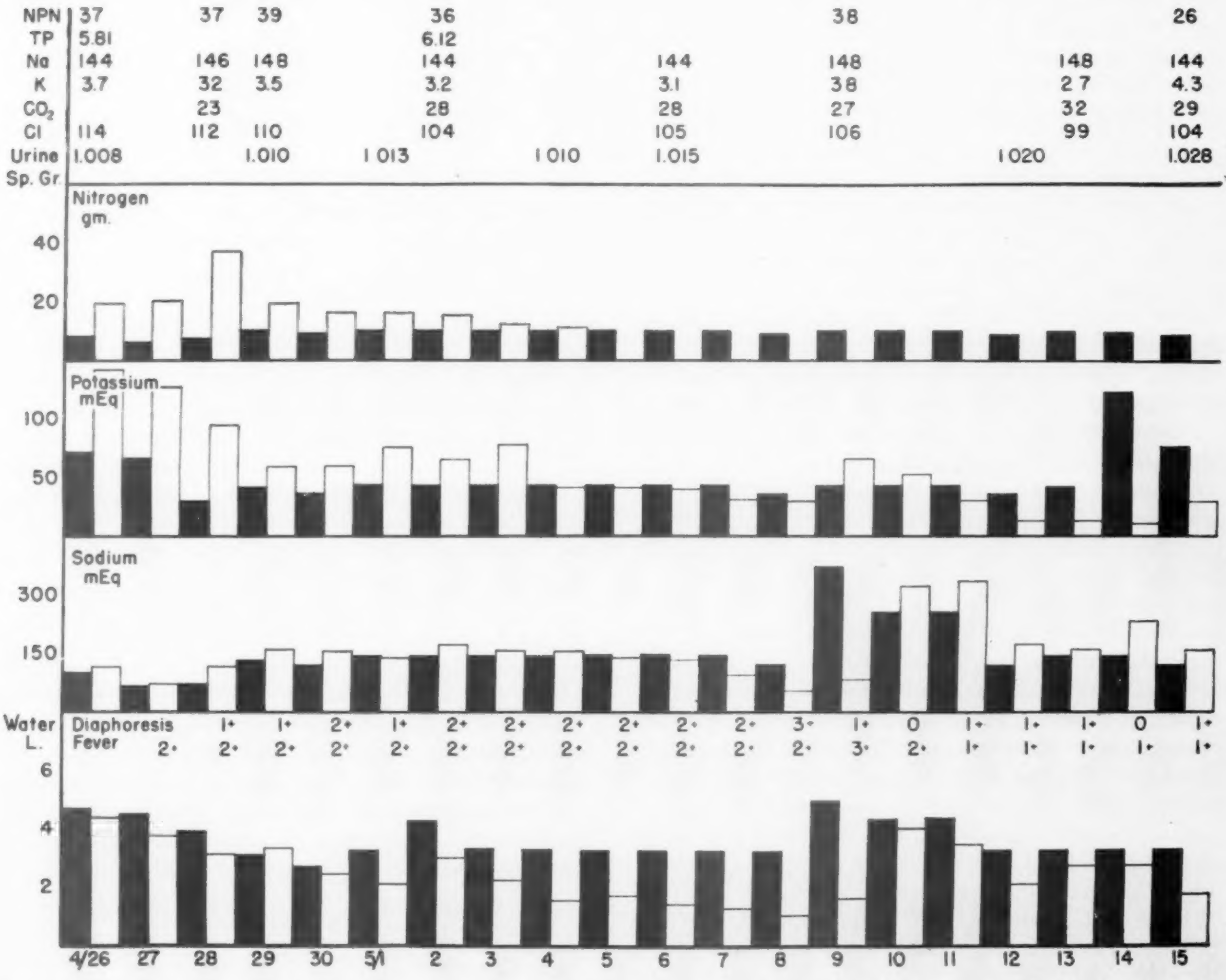

Fig. 3B. Case II. Development of hyperosmolarity of body fluids after serious craniocerebral trauma. Black columns indicate intake and white columns urinary output. Nitrogen output depicts urinary urea nitrogen only. Non-protein nitrogen (NPN) and creatinine (creat.) are expressed in mg./100 cc. Creatinine clearance ($C_{creat.}$) is a twenty-four hour endogenous creatinine clearance expressed in cc./minute. Total protein (TP), electrolytes, tachypnea, diaphoresis and fever are expressed as in Figure 1. Urine specific gravity is measured from the total twenty-four specimens. Urinary chloride excretion tends to follow the same pattern as the urinary sodium excretion.

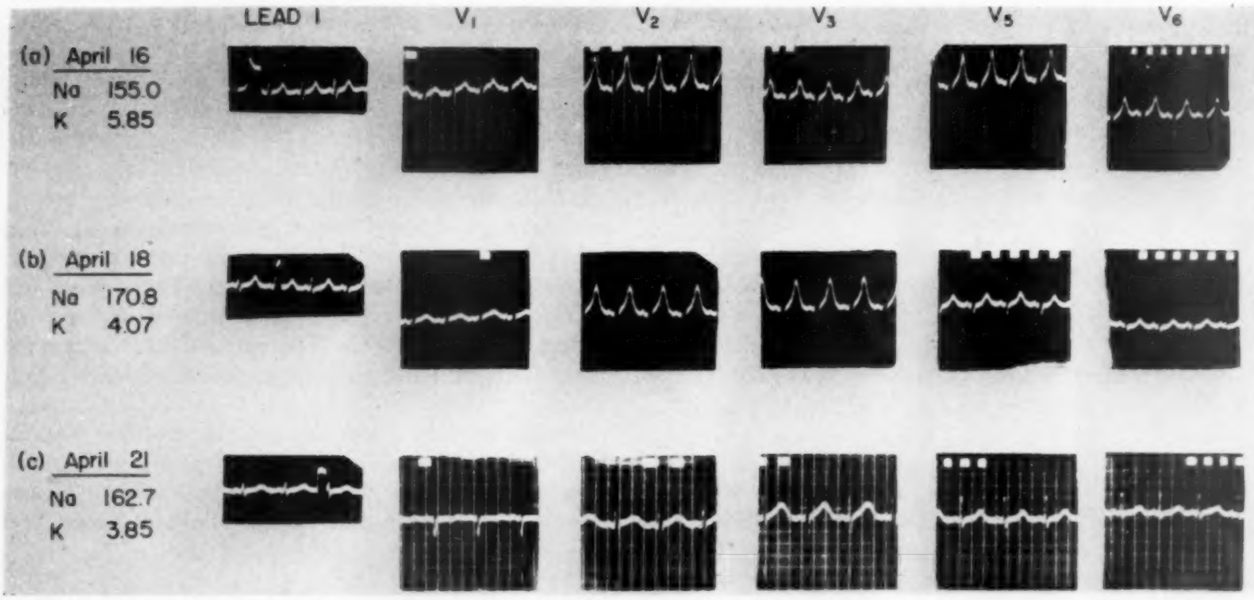

FIG. 4. Electrocardiographic changes in Case II. Plasma calcium normal in all cases. (a) Changes suggestive of slight hyperkalemia. Note the narrow, peaked T waves. (b) Forty-eight hours later—regression toward normal but still suggestive of minimal hyperkalemia. (c) Seventy-two hours later—changes suggestive of hypokalemia despite normal plasma potassium concentration. Note prolongation of Q-T interval, rounding of T waves and U waves in V2.

41 mEq. of potassium, 31 mEq. of sodium and 2,550 cc. of water. The average daily urinary volume was 1,590 cc. On April 14 the specific gravity was 1.009. Chemical studies were not made of the blood or urine. Diaphoresis was not striking, but the temperature ranged from 101° to 104°F. and there was a deep hyperpnea ranging from 24 to 44 respirations per minute. Blood pressure and pulse rate remained elevated and the patient remained deeply comatose.

Plasma electrolyte concentrations at 8:00 A.M. on April 16 were 150 mEq. of sodium, 7.4 mEq. of potassium, 13 mEq. of bicarbonate and 121 mEq. of chloride per L.; total proteins were 7.40 gm./100 cc. (Fig. 3A.) At 6:00 P.M. the patient appeared extremely dehydrated and blood pressure fell to 90/70 mm. Hg, but without signs of circulatory collapse. At this time non-protein nitrogen was 359 mg.; creatinine, 4.9 mg.; and plasma inorganic phosphorus, 11.6 mg./100 cc., with plasma electrolyte concentrations as shown in Figure 3A. An electrocardiogram revealed slight T wave changes compatible with hyperkalemia. (Fig. 4A.) During April 16 and 17 the patient received a total of 13,120 cc. of water and 928 mEq. of sodium as sodium chloride; he excreted 8,200 cc. of water and 135 mEq. of sodium in the urine. By April 18 the plasma sodium concentration reached a peak of 171 mEq./L. although skin turgor was greatly improved. The urinary sodium concentration at this time was only 15 mEq./L. and the urinary specific gravity was 1.012.

During the week of April 18 to 25 the patient received an average daily intake of 5,380 cc. of water and 60 mEq. of sodium. The plasma sodium concentration gradually decreased to the normal range. (Fig. 3A.) During this period the non-protein nitrogen, creatinine and plasma inorganic phosphorus all decreased to the normal range; endogenous creatinine clearance increased greatly; and the twenty-four hour urea clearance increased from 13 to 58 cc./minute. His pulse and respiratory rate decreased toward normal although the level of consciousness was unchanged. Of note is the strikingly negative potassium balance during this week. Electrocardiographic evidence suggestive of potassium deficiency occurred on April 21 (Fig. 4C) and hypokalemia was observed on April 22 and April 24. (Fig. 3A.) On April 26 two generalized seizures occurred. From May 2 to May 8 the urinary volume decreased, presumably as a result of increased sweating. (Fig. 3B.)

The patient's responsiveness began to increase late in April and improved in May. During June he had a rapid improvement in his sensorium and began to speak monosyllabically. His appetite was voracious and his vital signs became normal. Blood chemistry studies and urinary examinations were normal. He regained some use of the right extremities and was able to get about in a wheelchair. He was discharged to a veterans' hospital in August, 1952, at which time his ability to cerebrate was subnormal but improving.

COMMENTS

There are striking similarities between the two patients presented herein. Each patient suffered severe craniocerebral trauma and presumably frontal lobe injury, for each recovered with residual impairment of frontal lobe function. After ten to fifteen days characterized by very small

sodium intake, by probably inadequate potassium intake, excessive nitrogen intake and an inadequate water intake in the face of excessive water loss through skin and lungs, each patient had a striking hypernatremia, hyperchloremia, hyperkalemia, hyponatruria, azotemia and acidosis. Each patient manifested a rapid decrease in plasma potassium concentration to hypokalemic levels during the ensuing week, while the urinary potassium excretion exceeded the potassium intake.

"*Neurogenic Hypernatremia.*" The hypothesis that specific cerebral lesions may be responsible for neurogenic hypernatremia is supported by the work of Lewy and Gassman [*20*] who observed significant hyperchloremia in cats after stimulating unilaterally the paroptic nucleus of the hypothalamus. Stevenson et al. [*21*] have produced bilateral lesions in the ventromedian nuclei of the hypothalamus in rats and observed chronic hypodipsia and hypernatremia when the water intake was dependent upon oral consumption.

Clinically, the etiologic importance of cerebral damage in producing hypernatremia and azotemia is difficult to evaluate, for complete data on water and electrolyte balance in the reported cases are frequently lacking. McLardy [*22*] reported four deaths from uremia in the third week after a bilateral prefrontal leukotomy; all four patients had bilateral damage to the posterior orbital cortex at necropsy. Sweet et al. [*4*] have mentioned the likelihood that a lesion in the neighborhood of the third ventricle or posterior frontal lobe may cause hyperchloremia and azotemia. Further, in the great majority of the reported cases of neurogenic hypernatremia [*1–19*] the patients had involvement chiefly of the frontal lobe and/or hypothalamus. On the other hand, Welt et al. [*10*] point out that the development of severe water deficit and hypernatremia in the stuporous or comatose patient who has a neurologic disorder may be caused by his impaired ability to experience and express the sensation of thirst. Engstrom [*14*] believes that most of the reported cases are due to an impaired thirst mechanism, diabetes insipidus or both.

Water Deficit and Hypernatremia. In an excellent review article, Welt and his associates [*10*] outline the physiologic consequences of water deficit. They document evidence for an extremely well integrated series of responses by the organism which are oriented toward holding the sacrifice of fluid volume to an absolute minimum. The earliest and probably most important response to water deficit is an increase in the concentration of sodium in the extracellular fluid. There is an immediate transfer of water from the cells, permitting the intracellular compartment to contribute to the water deficit, and there is evidence that the resultant cellular dehydration decreases the rate of sweating and insensible perspiration as well as giving rise to the sensation of thirst. In addition, the hyperosmolarity of the extracellular fluid stimulates, presumably via a hypothalamic osmoreceptor, the secretion of antidiuretic hormone from the posterior pituitary, increasing the renal tubular reabsorption of water.

The decrease in volume of all the body fluids entails contraction of the plasma volume. This promotes increased renal tubular reabsorption of salt (presumably via a decrease in the volume of fluid in some key structure within the cranial cavity) and antidiuresis (also presumably via the posterior pituitary). A third consequence of body water deficit is an increase in the oncotic pressure of the plasma. Stimulation of a postulated "oncoreceptor" increases renal tubular reabsorption of both salt and water. A fourth consequence of body water deficit has recently been elucidated: increased adrenocortical secretion of 18-aldocorticosterone, which promotes sodium retention, potassium excretion and alkalosis [*36*].

Many of the features of these two cases can be adequately explained as predictable responses to a severe water deficit. Before recognition of the severe hyperosmolarity, both patients had a negative water balance. Both were febrile and tachypneic (presumably caused by involvement of the medullary respiratory center), and the patient in Case I had a profuse diaphoresis out of proportion to his fever (presumably caused by involvement of the hypothalamic center for temperature control). Although data were not available on urinary sodium excretion during this period, it is likely that this was quite small in each case, in view of the small sodium intake (average, 26 mEq./day) and continued loss of water through skin and lungs. The water deficit was perhaps enhanced in each case by a moderate protein intake, given at a time when each patient was probably experiencing the reaction to injury characterized by the inability to store nitrogen [*23*]. (The urea thus derived plus that from a probable negative nitrogen balance

would increase the solute load demanding renal excretion.)

The progressively greater water deficit produced oliguria and peripheral vascular collapse in the patient in Case I as his plasma volume decreased almost to a lethal level. It was at this point that the serum sodium concentration was found to be 192 mEq./L., and the urinary sodium concentration 21 mEq./L. In Case II the patient did not suffer as severe a water deficit and was found to have a serum sodium concentration of 150 mEq./L. (later increased to 171 mEq./L. by the excessive administration of salt) and a urinary sodium concentration of 12 mEq./L.

Thus both patients may be examples principally of water depletion. Elkinton and Taffel [*24*] deprived dogs of water and food until death and noted extremely low urinary sodium and chloride concentrations with serum sodium concentrations, terminally, as high as 186 mEq. and chloride 133 mEq./L. Borst [*25*] implicated an insufficient filling of the arterial system (as a result of decreased effective plasma volume) as the common denominator in various clinical instances of hyperchloremia and hypochloruria.

This avidly increased tubular reabsorption of salt as a response to contracted plasma volume has been described by Peters as the dehydration reaction [*26*]. The mechanism of this reaction is not clear but the experiments of Brun et al. [*27*], Harrison and his co-workers [*28*] and Strauss and his associates [*29*] suggest the existence of an intracranial structure concerned with the renal regulation of salt excretion. Harrison's group [*28*], by compressing the neck to occlude venous but not arterial flow, was able partially or completely to reverse the decreased rate of salt excretion produced (1) by sitting from the supine position and (2) by controlled bleeding. These data suggest the existence of an intracranial "volume receptor" within which a decrease of fluid volume acts as the stimulus for the increased tubular reabsorption of salt. An increased secretion of 18 aldocorticosterone or aldosterone might partially explain the intermediate mechanism here. Several studies have shown that the secretion of this salt-regulating hormone is dependent upon the extracellular fluid volume [*37*] and, more specifically, the intravascular volume [*36*]. (It is independent of total body sodium or of sodium concentration.) Welt [*30*] demonstrated that an intact adrenal cortex is a requisite to most of the increased tubular reabsorption of salt promoted by the passive erect posture.

In this regard, Leaf and his co-workers [*35,37*] have reported that prolonged administration of antidiuretic hormone (ADH) plus unrestricted fluid intake results in a decreased aldosterone excretion and an increased excretion of sodium chloride which they regard as the organism's normal volume-regulatory response to expansion; the response fails to appear when the volume expansion is prevented by fluid restriction. This increased sodium chloride excretion after ADH is diametrically opposed to the dehydration reaction of increased aldosterone excretion and decreased sodium chloride excretion; the two conditions could well represent the two extremes of the same regulation mechanism.

In short, the evidence suggests that the sodium chloride retention in the reported cases of neurogenic hypernatremia does not constitute a primary pathologic process but represents a normal response by the volume-regulating mechanisms of the organism. It would seem to make little difference to the organism whether the initial fluid deficit is caused by (1) impaired osmoregulation in the supraopticohyphophyseal system, and/or (2) excessive urea diuresis from increased catabolism of stress or from high-protein feeding mixtures [*10,38*], and/or (3) marked extrarenal water loss, as in the present cases. That cerebral lesions might lower the threshold of the proposed intracranial volume receptor (stimulating aldosterone secretion and increased tubular salt absorption) is, of course, a possibility.

It is evident that the unconscious neurosurgical patient is a candidate par excellence for the development of a water deficit with little or no salt deficit. Fever, diaphoresis and tachypnea are common occurrences, either from the central injury or secondary to complicating infection, and he is unable to experience and express the sensation of thirst. The magnitude of water loss through sweating is illustrated in Figure 1B. From February 29 through March 2 this patient's intake averaged 6,000 cc. daily and his urinary volume averaged only 800 cc. daily, yet at this time the room temperature was cool, the patient's fever was of a low grade and the tachypnea was no longer severe. Drenching diaphoresis was estimated to account for approximately 5 L. of water lost daily via the skin. Hyperventilation and fever have been reported

to initiate (in children) the train of events leading to hypernatremia [*13*].

Potassium Metabolism. The potassium data are of interest in these cases. At the time when the hyperosmolarity was discovered each patient had a hyperkalemia (8.7 and 7.4 mEq./L. respectively) and a hyperkaluria relative to the potassium intake (possibly mediated via aldosterone). The release of potassium in excess of nitrogen from the intact cell occurs during dehydration [*31*] and by decreasing cellular osmolar concentration may contribute more intracellular water to defend the extracellular fluid volume. It is noteworthy that narrow, peaked T waves were seen in the electrocardiogram (Figs. 2 and 4A), although hemoconcentration and increased cellular liberation of potassium were probably chiefly responsible for the hyperkalemia in each case.

Upon rehydration, hypokalemia developed in each patient within a week; however, in Case I the patient did not receive any potassium during the first four days of rehydration. (Fig. 1A.) In Case II the hyperosmolarity of the body fluids was further increased by excessive sodium administration (Fig. 3A) which may have enhanced the loss of cellular potassium [*31*]. (During this week the average daily potassium urinary output of 118 mEq. far exceeded the average daily intake of 58 mEq.)

Renal Factors. The presence of azotemia and acidosis without evidence of intrinsic renal disease is *a priori* evidence of renal insufficiency as a result of inadequate renal circulation. The degree of dehydration in these two patients was striking, and the normal urinalyses and normal renal function upon recovery would exclude underlying renal disease.

It is worthy of comment, however, that the patient in Case II (Fig. 3A) entered the hospital on April 7, ten hours after injury, with evidence of severe dehydration. With inadequate rehydration he gradually began to excrete a copious, dilute urine at a time when azotemia, acidosis and hypernatremia were developing (discovered April 16). Since acute renal failure has been observed in the absence of oliguria [*33,34*], it seems plausible to assume that this relatively copious and inefficient urine excretion was due to renal tubular damage secondary to the dehydration and renal ischemia. Indeed, Luetscher and Blackman [*2*], Goodale and Kinney [*3*], Swan and Merrill [*33*] and Doolan et al. [*39*] have all reported cases in which hyperchloremia and hypernatremia with low urinary concentrations of these ions were observed during the diuretic phase following acute renal failure, when tubular function was certainly still abnormal. Luetscher and Blackman [*2*] demonstrated the primary renal defect to be an inadequate tubular reabsorption of water in the face of continued electrolyte retention.

(One cannot with certainty ascribe the dilute, excessive urine flow in this case to renal tubular damage. It is possible to invoke a "urea diuresis." Perhaps the cerebral trauma produced a temporary diabetes insipidus or in some way impaired neurogenic renal control. However, the concept of renal tubular damage appears to be more valid.)

Whether or not renal water loss is excessive for any given patient's intake is impossible to evaluate without knowing the approximate respiratory and skin water losses. A rather low urinary specific gravity and/or "normal" urinary flow recorded for some of the reported cases of neurogenic hypernatremia may not be proof of a "good state of hydration" if a patient is febrile, sweating or hyperpneic, or if dehydration had developed before the initial studies. Under these circumstances a normal urine volume might indicate a diabetes insipidus-like state or renal tubular damage.

Clinical Implications. It is evident that severe dehydration and its sequelae might account, in two cases presented, for the hypernatremia, hyponatruria, hyperkaluria, azotemia and acidosis. Although most authors emphasize the absence of clinical dehydration, unrecognized water deficit might also be invoked to explain similar findings in the reported cases; since water loss is mainly intracellular, physical signs of dehydration may not be apparent unless there is concomitant (late) extracellular shrinkage.

From the point of view of management, it is essential that the patient who has severe craniocerebral trauma be watched closely for excessive extrarenal water loss through skin or lungs, and for renal water loss that may be excessive under the circumstances. An average daily fluid intake of 2 or 3 L. may easily be inadequate. It is suggested that, during the immediate post-trauma period, the serum electrolytes and non-protein nitrogen be checked at least twice weekly if possible; an increasing sodium or non-protein nitrogen concentration may be early evidence of a water deficit and may be corroborated by an increase in the plasma protein concentration and

hematocrit level. Should a water deficit be detected, protein intake should be minimized so as to diminish the solute load presented to the kidneys for excretion. Sodium and potassium intake should be gauged from the plasma level and the urinary excretion of these ions. (Testing only for urinary sodium or chloride concentration may be dangerously misleading in the patient who has hyperchloremia and hypochloruria.) In cases in which diabetes insipidus or an impaired thirst mechanism is suspected the administration of pitressin® is indicated [*14*].

SUMMARY

Two cases have been presented in detail in which hypernatremia, hyperkalemia, azotemia and acidosis developed in comatose patients after severe craniocerebral trauma. Both patients excreted small urinary concentrations of sodium but rather large quantities of potassium. Clinical and chemical improvement occurred after rehydration but hypokalemia developed in each case. Both patients had functional impairment of the frontal lobe after prolonged convalescence.

The hyperosmolarity, azotemia and hyponatruria in each case could be explained as a normal physiologic response to severe water deficit (induced via fever, sweating and hyperventilation) with possible secondary renal tubular damage. Evidence is reviewed that salt retention represents a normal response by volume-regulating mechanisms to a fluid deficit caused either by (1) impaired osmoregulation in the hypothalamus or hypophysis and/or (2) marked renal or extrarenal water loss. It is suggested that the unconscious patient who has a brain injury is prone to the development of unrecognized water deficit which might in some cases be detected only by frequent chemical analyses of the blood.

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An Abnormality in Renal Function Resulting from Urinary Tract Obstruction*

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ONE of the most remarkable properties of the normal kidney is its capacity to control the volume and composition of extracellular fluid. This is accomplished by precise regulation of the amounts of sodium chloride and water excreted in the urine. Although the mechanisms involved in this regulatory function are complicated and are most certainly dependent upon extrarenal factors, control must finally reside in the nephron itself. It should be anticipated, therefore, that in certain forms of intrinsic renal disease, inordinate urinary losses of salt and water may occur. Among the entities in which this abnormality has been noted are salt-losing nephritis and the diuretic phase of acute tubular necrosis. In addition, limitation in the capacity of the kidneys to conserve salt and water may be observed in most patients with far advanced Bright's disease. In the present discussion, observations are presented on an abnormality in renal salt and water conservation occurring after the relief of acute urinary retention. The data suggest that this state, like those listed, is a manifestation of intrinsic renal disease which in this instance is an acquired and self-limited nephropathy.

Investigations of the defects in electrolyte and water excretion in renal salt-wasting syndromes have been limited by the fact that renal function is often so deteriorated that the usual quantitative relationships between clearance values and discrete renal functions may no longer obtain. In the cases to be described the values for inulin clearance were only moderately depressed and could reasonably be equated with glomerular filtration rates. An attempt has therefore been made to determine the nature and site of the defect in solute and water excretion, utilizing current physiologic interpretations. The possibility that a similar defect may exist in other renal salt-wasting syndromes is suggested by the fact that they demonstrate certain of the same functional patterns noted in the present patients.

METHODS

Data were obtained in four patients in whom acute renal failure developed secondary to mechanical obstruction of the urinary tract. Clearance studies were conducted in each patient during the polyuric phase which followed relief of the obstruction. In Cases I and II studies were repeated after subsidence of polyuria.

CASE REPORTS

CASE I. (Tables I and II.) A sixty year old white woman was admitted to the hospital because of anuria of four days' duration. Six years prior to admission a left ureteral calculus was removed by instrumentation. Because of the subsequent development of a staghorn calculus, a left nephrectomy had been performed twenty months prior to admission. The histologic appearance of the resected kidney was consistent with chronic pyelonephritis. Sixteen months prior to admission ureteral colic led to the discovery of a non-opaque right ureteral calculus which allegedly was passed spontaneously. Three weeks prior to admission anorexia and nausea became prominent and were followed within a week by vomiting. For the four-day period preceding admission the patient was hospitalized in a local hospital where her urinary output did not exceed 30 ml./twenty-four hours.

On admission, the patient was clinically uremic and showed evidence of mild congestive heart failure. Catheterization of the right ureter disclosed an obstruction at the ureteropelvic junction which was bypassed, and approximately 100 ml. of urine were obtained from the renal pelvis. During the first twelve

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TABLE I

CASE I, INITIAL STUDY: C_{in}, C_{PAH}, C_{urea}, IN U/P, AND URINE FLOW

Per	Time Elapsed (min.)	C_{in} (ml./min.)	C_{PAH} (ml./min.)	F.F. (%)	C_{urea} (ml./min.)	C_{urea}/C_{in} (%)	In U/P	V (ml./min.)	V/wC_{in} (%)
Priming Injection of Inulin and PAH and Initiation of Sustaining Solution (at —Forty Minutes)									
1	0–15	28.4	59.7	47.6	24.7	87	3.4	8.3	31.4
2	15–30	29.9	72.3	41.4	24.6	82.3	3.5	7.9	28.4
3	30–46	30.7	69.9	43.9	27.3	88.9	3.4	8.4	29.4
100 mμ. Pitressin by Single Injection and 1 mμ./min. Infused in Sustaining Solution (at Fifty-one and One-half Minutes)									
4	70–85	30.2	70.7	42.7	....	....	4.1	6.9	24.6
5	85–100	31.8	71.1	44.7	....	....	4.4	6.7	22.6
6	100–115	26.2	67.5	38.8	....	....	4.2	5.8	23.8

NOTE: One liter of water was administered approximately ninety minutes before the priming injection. The sustaining solution contained Na, 141 mEq./L; Cl, 125 mEq./L; and HCO_3, 16 mEq./L. and was delivered at a rate of 8 ml./minute.

C_{in} = inulin clearance.
C_{PAH} = PAH clearance.
F.F. = filtration fraction.
C_{urea} = urea clearance.
In U/P = urine/plasma ratio for inulin. In calculating the inulin U/P ratio, P was corrected for plasma water content.
V = urine flow.
w = correction for plasma water.
V/wC_{in} = percentage of filtered water excreted.

TABLE II

CASE I, INITIAL STUDY: SOLUTE AND WATER EXCRETION

Per	C_{in} (ml./min.)	$U_{Na}V$ (μEq./min.)	$U_{Na}V/FL$ (%)	$U_{Cl}V$ (μEq./min.)	$U_{Cl}V/FL$ (%)	U_KV (μEq./min.)	U_KV/FL (%)	C_{Osm} (ml./min.)	C_{Osm}/wC_{in} (%)	Elect C_{Osm} (ml./min.)	Elect C_{Osm}/C_{Osm} (%)	C_{H_2O} (ml./min.)	T^dO_{sm} (μOsm./min.)	T^dO_{sm}/FLO_{sm} (%)
1	28.4	764	20.7	685	21.6	120	109.4	7.4	27.8	5.3	71.3	0.95	283	3.3
2	29.9	735	19.3	666	19.6	119	138	7.2	25.8	5.1	70.9	0.72	214	2.4
3	30.7	790	20.2	777	22.5	109	123.5	7.4	25.7	5.6	75.7	1.04	310	3.4
4	30.2	731	19.1	759	22.3	135	134	7.2	25.6	5.5	76.4	−0.33	...	...
5	31.8	730	18.0	632	17.7	131	130.4	6.9	23.3	5.1	74	−0.18	...	...
6	26.2	667	19.9	553	18.8	107	142	6.2	25.4	4.5	72.6	−0.36	...	...

NOTE: Filtered loads (FL) of electrolytes are corrected for appropriate Donnan factors.

$U_{elect}V/FL$ = percentage of filtered load excreted (alternatively expressed as C_{elect}/C_{in}).
C_{Osm} = osmolar clearance.
Elect C_{Osm} = electrolyte osmolar clearance (see text for calculation).
Elect C_{Osm}/C_{Osm} = fraction of osmolar clearance due to electrolytes.
C_{H_2O} = free water clearance.
T^dO_{sm} = distal solute reabsorption (see text).
FLO_{sm} = filtered load of osmols.

hours after placement of an inlying ureteral catheter the urine volume exceeded 7.5 L. and the sodium excretion equaled 700 mEq. During the subsequent twenty-four hours, 13 L. of urine containing 1,140 mEq. of sodium were excreted. On the following day (day of initial clearance studies), the urine volume totalled 9.5 L. and the sodium excretion was 800 mEq. During the succeeding ten days both urinary output and sodium excretion rates decreased slowly toward normal levels. Follow-up studies were performed on the eleventh hospital day. On the sixteenth hospital day a large uric acid stone was surgically removed

TABLE III

CASE II, INITIAL STUDY: C_{in}, C_{PAH}, C_{urea}, IN U/P, AND URINE FLOW

Per	Time Elapsed (min.)	C_{in} (ml./min.)	C_{PAH} (ml./min.)	F.F. (%)	C_{urea} (ml./min.)	C_{urea}/C_{in} (%)	In U/P	V (ml./min.)	V/wC_{in} (%)
Priming Injection of Inulin and PAH and Initiation of Sustaining Solution (at —Forty-seven Minutes)									
1	0–15	19.6	94.5	20.7	15.9	81	3.5	5.1	28.2
2	15–31	19.2	94.6	20.3	15.7	81.8	4.3	4.2	23.4
3	31–47	19.5	89.4	21.8	14.8	76	4.4	4.1	22.5
100 mμ. Pitressin by Single Injection and 1 mμ./minute Infused in Sustaining Solution (at Fifty-three Minutes)									
4	68–83	16.9	82.7	20.4	16.2	96	5.4	2.9	18.6
5	83–98	19.6	89.2	21.9	19.0	97	4.7	3.9	21.4
6	98–123	18.0	94.2	19.1	18.8	104	4.4	3.8	22.8

NOTE: 800 ml. of water were administered approximately ninety minutes before the priming injection and supplementary water was given during the control periods. Sustaining solution (see Table I for composition) was delivered at 5.0 ml./minute.
See Table I for definition of symbols.

TABLE IV

CASE II, INITIAL STUDY: SOLUTE AND WATER EXCRETION

Per	C_{in} (ml./min.)	$U_{Na}V$ (μEq./min.)	$U_{Na}V/FL$ (%)	$U_{Cl}V$ (μEq./min.)	$U_{Cl}V/FL$ (%)	U_KV (μEq./min.)	U_KV/FL (%)	C_{Osm} (ml./min.)	C_{Osm}/wC_{in} (%)	$U_gV/U_{Osm}V$	$U_{urea}V/U_{Osm}V$	Elect C_{Osm} (ml./min.)	Elect C_{Osm}/C_{Osm} (%)	C_{H_2O} (ml./min.)	T^d_{Osm} (μOsm./min.)	T^d_{Osm}/FL
1	19.6	185	7.8	243	12.1	77	94.8	3.2	17.6	5.9	31.6	1.81	56.6	1.93	538	12.8
2	19.2	132	5.4	163	7.9	64.8	81.5	2.6	14.5	5.3	38	1.29	49.6	1.58	442	10.4
3	19.5	140	5.7	168	8.0	61.1	75.7	2.7	14.7	2.4	34.9	1.31	49.3	1.41	398	9.1
4	16.9	103	4.8	128	7.1	58	83	2.1	13.5	1.5	41.7	1.04	49.5	0.8	...	....
5	19.6	150	6.2	185	8.9	68.3	84.1	2.7	14.8	2.5	42.8	1.44	53.2	1.2	...	....
6	18.0	158	6.9	188	9.5	78	102	2.7	16.2	1.6	43.9	1.52	54.3	1.1	...	....

NOTE:
$U_gV/U_{Osm}V$ = mM/min. glucose excretion/mM/min. total osmol excretion;
$U_{urea}V/U_{Osm}V$ = mM/min. urea excretion/mM/min. total osmol excretion.
See Table II for remainder of definitions.

from the ureteropelvic junction and several smaller stones of similar composition were taken from the inferior calyces.

The blood urea nitrogen level was 232 mg. per cent on admission, 70 mg. per cent at the time of initial clearance measurements, and 24 mg. per cent at the time of follow-up clearance measurements. At the time of the patient's discharge (six weeks after admission) the blood urea nitrogen was 20 mg. per cent.

Case II. (Tables III and IV.) A seventy-six year old white man was admitted to the hospital with a history of frequency and nocturia of several years' duration. Three weeks prior to admission these symptoms increased and dysuria appeared. Six days prior to admission overflow incontinence was noted. The pertinent past history included mild diabetes for five years, well controlled on diet alone, and arteriosclerotic heart disease with mild congestive heart failure, treated effectively with digitalis and intermittent mercurial diuretics.

On admission the patient was somnolent and clinically dehydrated. His bladder was palpably distended and his prostate was markedly enlarged. Catheterization of the bladder was followed by the development of marked polyuria. The urine volume totalled 3.1 L. during the first eight hours and 7.4 L. during the next twenty-four hours. Sodium excretion during the latter period was 274 mEq. During the subsequent twenty-four hours the urine volume reached its maximum value of 9.4 L. and contained 350 mEq. of sodium. Thereafter urine volumes and

TABLE V

CASE III, C_{in}, C_{PAH}, $C_{I^{131}}$, IN U/P, URINE FLOW AND ELECTROLYTE EXCRETION

Per	Time Elapsed (min.)	C_{in} (ml./min.)	C_{PAH} (ml./min.)	F.F. (%)	$C_{I^{131}}$ (ml./min.)	$C_{I^{131}}/C_{in}$ (%)	In U/P	V (ml./min.)	V/wC_{in} (%)	$U_{Na}V$ (µEq./min.)	$U_{Na}V/FL$ (%)	$U_{Cl}V$ (µEq./min.)	$U_{Cl}V/FL$ (%)	U_KV (µEq./min.)	U_KV/FL (%)
Priming Injection of Inulin PAH and I^{131} and Initiation of Sustaining Solution (at — Thirty-two Minutes)															
1	0–15	65.7	283	23.2	40.2	60.7	6.9	7.6	12.5	1015	12	970	12	94.6	41
2	15–30	67.8	304	22.3	41.1	60	5.7	9.8	14.3	1088	12	1004	13	98.6	41
3	30–45	64.3	294	21.9	39.3	60.7	5.3	9.9	15	1170	14	1110	14	99.9	44
Injection of 10 mg. of DOCA (at Thirty-three Minutes)															
4	135–150	48.8	328	14.9	26.8	54.8	12.8	2.2	4.8	367	6	354	4	74	45
5	150–165	62.3	465	13.4	35.3	56.4	14.2	2.8	4.5	463	6	447	6	93.8	44
6	165–180	67.0	496	13.5	38.4	57.0	12.8	3.6	5.4	595	7	607	8	110	49

NOTE: One liter of water was administered approximately an hour before priming injection and supplementary water was given during the course of the experiment. Sustaining solution was delivered in a physiologic saline vehicle at 1.5 ml./minute.
$C_{I^{131}}$ = I^{131} clearance. See preceding tables for additional definitions.

TABLE VI

CASE IV, C_{in}, C_{PAH}, C_{urea}, IN U/P, AND URINE FLOW

Per	Time Elapsed (min.)	C_{in} (ml./min.)	C_{PAH} (ml./min.)	F.F. (%)	C_{urea} (ml./min.)	C_{urea}/C_{in} (%)	In U/P	V (ml./min.)	V/wC_{in} (%)
Priming Injection of Inulin and PAH and Initiation of Sustaining Solution (at — Forty-four Minutes)									
1	0–23	46.1	184	25.4	32.6	70	11.3	3.8	8.7
2	23–43	37.5	157	23.9	32.0	85	8.2	4.25	12.2
3*	43–58	42.9	158	27.0	29.2	68.5	7.7	5.2	13.1
100 mµ. Pitressin by Single Injection and 1 mµ./minute Infused in Sustaining Solution (at Fifty-eight Minutes)									
4	58–77	44.5	169	26.3	34.8	78.2	6.9	6.0	14.4
5	77–93	43.8	190	23.1	33.1	75.6	6.8	6.0	14.7
6	93–112	49.1	223	21.8	38.4	78.5	6.5	7.0	15.3
7	112–129.5	47.4	277	17.3	39.5	83.3	5.9	7.5	17.0

NOTE: See Table I for details of water administration. Sustaining solutions were delivered in a normal saline vehicle at 5 ml./minute. See preceding tables for definition of symbols.
* Patient experienced chilly sensations without fever for about fifteen minutes.

sodium excretion fell slowly toward normal limits. Two months after catheterization the patient was readmitted for prostatectomy and his urinary output varied (in accordance with his intake) between 900 and 2,000 ml./day. Initial clearance studies were conducted during the day of maximal diuresis. Follow-up studies were made during the second admission.

The blood urea nitrogen was 177 mg. per cent on admission, 50 mg. per cent on the day of initial clearance measurements and 27 mg. per cent at the time of follow-up studies.

CASE III. (Table V.) A seventy-six year old white man was admitted to the hospital for gangrene of the right lower extremity. His initial non-protein nitrogen level and urinalysis were normal. Two weeks after admission his right leg was amputated below the knee and three weeks thereafter a second amputation was performed above the right knee. Six days following the second procedure the patient was noted to have complete urinary suppression, the duration of which was estimated retrospectively to be forty-eight hours. Subsequent to the establishment of effective catheter drainage of the bladder an extreme and sustained

TABLE VII

CASE IV, SOLUTE AND WATER EXCRETION

Per	C_{in} (ml./min.)	$U_{Na}V$ (μEq./min.)	$U_{Na}V/FL$ (%)	$U_{Cl}V$ (μEq./min.)	$U_{Cl}V/FL$ (%)	U_KV (μEq./min.)	U_KV/FL (%)	C_{Osm} (ml./min.)	C_{Osm}/wC_{in} (%)	$U_{urea}V/U_{Osm}V$ (%)	Elect C_{Osm} (ml./min.)	Elect C_{Osm}/C_{Osm} (%)	C_{H_2O} (ml./min.)	T^cH_2O/wC_{in} (%)
1	46.1	241	4.1	279	5.5	127	78.4	4.3	9.9	64	2.2	50	−.5	1.1
2	37.5	400	8.4	417	10.4	151	99.4	5.1	14.6	52	3.2	63	−.85	2.3
3	42.9	541	9.6	545	12.0	151	95.4	6.1	15.4	40	4.1	67	−.9	2.2
4	44.5	636	11.0	653	13.7	163	96.9	6.9	16.7	42	4.8	70	−.9	2.2
5	43.8	654	11.5	692	14.6	171	100.8	7.2	17.7	39	5.1	71	−1.2	3.0
6	49.1	763	11.8	776	14.5	179	106.6	8.1	17.8	40	5.8	72	−1.1	2.4
7	47.4	803	13.1	817	15.8	199	129	8.5	19.3	39	6.0	71	−1.0	2.3

NOTE: T^cH_2O ($C_{Osm} - V$) is the expression for the ml./minute of solute-free water abstracted in the elaboration of a hypertonic urine. See preceding tables for definitions of other symbols.

polyuric state developed. For a period of three and one-half months the urinary output varied from 8.6 to 15 L./twenty-four hours, and the twenty-four hour excretion of sodium ranged from 900 to 1,900 mEq. Neither fluid restriction, pitressin,® nor DOCA® (5 mg. three times a day) materially influenced the volume or composition of the urine. Subsidence of polyuria ultimately occurred spontaneously and upon discharge urine volumes were less than 3 L./twenty-four hours. Clearance studies were made eight weeks after onset of the diuretic state.

The non-protein nitrogen on admission was 21 mg. per cent. The day after the onset of polyuria it was 76 mg. per cent, and three weeks later a similar value was recorded. Thereafter values for both non-protein nitrogen and creatinine decreased to normal limits.

CASE IV. (Tables VI and VII.) A fifty-five year old white man was admitted to the hospital with a prolonged history of nocturnal incontinence and difficulty in starting the urinary stream. During the two-month period preceding admission he noted persistent anorexia, weight loss, thirst and lassitude. Several weeks prior to admission frank dysuria, urgency and frequency developed. On admission the bladder was distended and the prostate markedly enlarged. He was noted to have moderate pitting peripheral edema. Catheterization of the bladder was followed by rapid accumulation of 1,250 ml. of urine. Although the ensuing diuretic state was less marked than in the other subjects (maximum recorded output, 4.5 L./twenty-four hours), the patient was not able to decrease his output in response to fluid restriction during the first two weeks after catheterization. On the thirty-fifth hospital day he underwent prostatectomy and at the time of discharge his urinary output was determined by his intake. Clearance studies were conducted fourteen days after the onset of the diuretic state.

The blood urea nitrogen was 58 mg. per cent on admission, 80 mg. per cent at the time of clearance studies and 16 mg. per cent upon discharge (fortieth hospital day).

PROCEDURE

Renal clearances were performed according to standard methods, the general details of which have been previously reported [*1*].

After administration of the priming injection of inulin and PAH and initiation of the sustaining infusion, an equilibration period of from thirty to forty-five minutes was allowed before beginning the first clearance period. In Case I, urine from the solitary kidney was collected through an inlying ureteral catheter. Simultaneous bladder catheterization was employed to assure complete collections; however, no appreciable amounts of urine appeared in the bladder. In Cases II and IV urine was collected through inlying bladder catheters and collection periods were concluded with air injections and suprapubic compression. Washouts with water were omitted in the interests of increasing the accuracy of the osmolality determinations. In Case III, freezing point depressions were not determined and urine collections were concluded with two 10 ml. washouts of distilled water and two or more air injections.

Heparinized venous blood samples were collected through an inlying needle at the midpoint of each period. These were centrifuged immediately and the plasma removed without delay.

Inulin was determined according to the method of Roe, Epstein and Goldstein [*2*]; PAH according to the method of Smith et al. [*3*]; urea according to the method of Archibald [*4*]; chloride according to the method of Van Slyke and Hiller [*5*]; sodium and potassium were

determined by internally compensated Baird and Barclay flame photometers; osmolality was determined by a Fiske osmometer, and glucose was determined according to the glucose oxidase method of Froesch and Renold [*6*]. Correction factors used in calculations were as follows: plasma water content (w) = 0.93;* Donnan factor for sodium, 0.95; chloride, 1.07; potassium, 0.90.

RESULTS

Initial Studies

Renal Hemodynamics. Values for glomerular filtration rate ranged from 20 to 66 ml./minute. Effective renal plasma flow was measured in three patients. In two patients (Cases II and IV) the depression of clearance values was proportional to that of glomerular filtration rate. In Case I, however, the value for effective renal plasma flow was disproportionately low (filtration fraction = 44 per cent) suggesting impaired tubular function with a decrease in PAH extraction.

Urine Flow. The values for twenty-four-hour urine volumes are recorded in the case reports. During the clearance studies, maximal urine flows, when expressed as percentages of the filtered water, ranged from 15 to 31 per cent. That these high values could not be attributed either to water diuresis or to "water-losing nephritis"† is apparent in the three patients in whom osmolality measurements were performed. Thus, whereas in pure water diuresis (i.e., water diuresis without simultaneous osmotic diuresis) the urine consists predominantly of free water, in Cases I and II the free water clearance (C_{H_2O}) constituted only 11 and 37 per cent of the respective urine flows, and in Case IV C_{H_2O} was negative throughout. The major portion of the urine volume in each patient therefore was osmotically obligated as evidenced by the fact that the osmolar clearances ranged from 63 per cent to over 100 per cent of the values for urine flow.

Urea/Inulin and I^{131}/Inulin Clearance Ratios. Urea clearances were measured in three patients and I^{131} clearance in the fourth. Values for urea clearances in all patients were inordinately high when compared to the simultaneous values for glomerular filtration rate. In Case IV a progressive increase in the urea/inulin clearance ratio occurred during the period of study. In Case III, I^{131} clearance was considerably higher than would be predicted for the level of the filtration rate.

Solute Excretion. In Cases I and II values for osmolar clearances averaged 15.6 per cent and 26.4 per cent of the filtered water. In Case IV the value initially was 9.9 per cent but it increased progressively to a final value of 19.3 per cent. The fraction of the osmolar clearance attributable to electrolytes in Cases I and II was 73 and 52 per cent, respectively. In Case IV this figure rose from 50 to 72 per cent.

Values for the minute rates of sodium excretion during the clearance studies are included in Table II, IV, V and VII. The percentage of filtered sodium excreted ranged from 6.3 per cent in Case II to 20 per cent in Case I. In Case IV this ratio increased from 4.1 per cent during the first clearance period to 13.1 per cent during the final period. Values for the percentage of filtered chloride excreted tended to be slightly higher than those for sodium. The percentage of filtered potassium excreted ranged from 41 per cent to 142 per cent and approached or exceeded unity in three of the four patients.

In Case III the administration of 10 mg. of DOCA subcutaneously was associated with a marked decrease in urine flow, sodium and chloride excretion rates, and an increase in potassium/inulin clearance ratios. This will be referred to again.

Follow-up Studies

Follow-up studies were made in two patients after subsidence of polyuria. (Table VIII.) Improvement was noted in values for glomerular filtration rate, renal plasma flow (measured in only one patient), concentrating ability, and electrolyte and water excretion. The marked degree of the improvement in solute and water excretion becomes apparent when the response to experimental induction of osmotic diuresis is examined. In both patients a non-electrolytic solute (mannitol) which characteristically produces progressive increases in the excretion rates of sodium, chloride and water was infused at a brisk rate. The percentage of the filtered loads of these substances excreted did not equal the

* The value for plasma water content was determined in Case III and assumed in the other cases. No attempt was made to estimate the change in (w) occurring during mannitol loading in the two follow-up studies. (Table VIII.)

† Earley [7] has recently described a six month old infant with obstructive uropathy and an associated polyuric state in whom the abnormality was attributed to "an acquired, reversible renal tubular unresponsiveness to the antidiuretic hormone."

TABLE VIII

FOLLOW-UP STUDIES

Per	Time Elapsed (min.)	C_{in} (ml./min.)	V (ml./min.)	V/wC_{in} (%)	In U/P	C_{PAH} (ml./min.)	C_{urea}/C_{in} (%)	$U_{Na}V$ (μEq./min.)	$U_{Na}V/FL$ (%)	$U_{Cl}V/FL$ (%)	U_KV/FL (%)	C_{Osm}/wC_{in} (%)	Elect C_{Osm}/C_{Osm} (%)	C_{H_2O} (ml./min.)	T_{Osm}^d/FL (%)
Case I. *Priming Injection of Inulin and PAH at −Forty-two Minutes; Inulin, PAH, Mannitol Sustaining Solution (at −Forty Minutes)*															
1	0–15	39.7	5.3	14.4	7.0	324	78	315	6.6	7.8	185	16.8	53.1	−0.9	....
2	15–30	44.0	6.3	15.4	6.5	315	69	387	7.3	8.8	148	17.8	49.3	−1.0	....
3	30–45	42.1	6.8	17.4	5.8	297	77	391	8.0	9.6	191	19.9	51.2	−1.0	....
100 mμ Pitressin by Single Injection and 1 mμ./minute Infused in Sustaining Solution (at Forty-six Minutes)															
4	65–80	45.9	8.7	20.4	4.9	316	72	505	9.4	13.3	204	23.7	51.3	−1.4	....
5	80–95	46.2	9.5	22.1	4.5	317	85	542	10.4	12.4	210	25.1	48.2	−1.3	....
6	95–100	46.6	10.3	23.7	4.2	333	76	649	12.3	13.8	185	26.5	47.8	−1.2	....
Case II. *Priming Injection of Inulin and PAH and Initiation of Sustaining Solution (at −Thirty-eight Minutes)*															
1	0–14	39.9	3.9	10.5	9.9	...	75	187	3.7	4.1	34.5	8.1	50.4	0.9	2.25
2	14–29	46.8	4.2	9.7	10.3	...	73	202	3.5	3.8	31.6	7.8	48.3	0.8	1.72
3	29–45	35.6	4.4	13.3	7.5	...	73	180	4.0	4.4	36.5	8.8	50.4	1.5	4.13
50 mμ. Pitressin by Single Injection at Forty-five Minutes; 1 mμ./minute Pitressin and Mannitol Infused in Sustaining Solution (at Forty-six Minutes)															
4	75–90	40.7	4.9	13.0	7.7	...	69	314	6.3	7.1	41.3	13.2	48.8	−0.1	....
5	90–107	45.3	4.8	11.4	8.7	...	60	293	5.3	6.0	32.0	11.4	46.9	±0	....
6	107–121	42.0	5.5	11.2	7.1	...	65	341	6.6	7.6	36.6	14.3	46.4	−0.1	....
7	121–135	39.8	5.3	11.3	7.0	...	58	334	6.8	7.8	34.4	14.9	45.9	−0.2	....

NOTE: Case I. See Table I for details of water administration. Sustaining solution was delivered in a normal saline vehicle at 8 ml./minute. Mannitol was administered throughout the study at 840 mg./minute. CASE II. See Table III for details of water administration. Sustaining solution A (periods 1 to 3) was delivered in a vehicle of 0.45 per cent saline and 2.5 per cent dextrose at 3.0 ml./minute. Sustaining solution B (containing mannitol, 840 mg./minute) was delivered in the same vehicle at 8.0 ml./minute. See preceding tables for definitions of symbols.

respective values recorded during the phase of spontaneous polyuria.

COMMENTS

Sudden impairment of the ability of the kidneys to conserve salt and water may result in serious losses of extracellular fluid. In the absence of judicious replacement therapy, these losses may ultimately impose life-threatening physiologic derangements. In the present patients an abnormality in renal function, associated with excessive salt and water excretion, resulted after relief of mechanical obstruction of the urinary tract. In two of the four patients the obstruction was due to prostatic hypertrophy. In another an inlying bladder catheter became occluded and in the fourth a ureteral calculus obstructed flow from a solitary kidney.

Clinically the syndrome was characterized initially by anuria, symptoms and signs of uremia, and chemical evidence of marked renal insufficiency. Differentiation from other forms of acute renal failure, including acute tubular necrosis, was facilitated by the presence of total anuria and in three cases by palpable bladder distention. The state of hydration prior to decompression varied from overt dehydration to frank edema and presumably reflected the antecedent fluid administration. Immediately following relief of obstruction by appropriate instrumentation, a polyuric state became manifest. The duration of this varied from several days to three and a half months. In three patients the urinary losses were formidable and in all patients it was necessary to replace urinary losses for a minimum of several days, in order to prevent depletion of extracellular fluid volume.

Although the development of a polyuric state following the relief of obstruction of the urinary tract has been previously documented [*8*], the mechanisms of the diuresis remain poorly defined. It is the intent of this discussion to consider observations which may help to extend knowledge regarding these mechanisms. Many of the findings in the present patients have also

been noted in other renal salt-wasting syndromes and in chronic Bright's disease. It is suggested, therefore, that qualitatively similar abnormalities in electrolyte excretion may occur in other patients with renal disease who demonstrate impaired ability to conserve salt and water.

Nature of the Diuresis. The characteristics of the diuresis in the present patients paralleled those observed in normal subjects when proximal tubular reabsorption of water is depressed by administration of an exogenous loading solute (i.e., during osmotic diuresis). Three groups of data illustrate this point.

Inulin urine/plasma (U/P) ratios: The progressive concentration of inulin as it courses down the nephron occurs as a function of water reabsorption. According to current evidence [*9*] about $\frac{7}{8}$ of the filtered water is reabsorbed in the proximal tubule and thus at the end of this segment the inulin U/P ratio approximates 8. Any additional reabsorption of water in the distal tubule will of course further increase the U/P ratio; however, suppression of distal tubular water reabsorption (e.g., during maximum water diuresis) is not typically associated with inulin U/P ratios appreciably below 8. The only way in which values below this level may routinely be achieved is by suppressing proximal water reabsorption. Experimentally this can be accomplished by the introduction, into the plasma and thus the glomerular filtrate, of a poorly reabsorbed osmotically active solute, such as mannitol or urea. In the presence of such diuresis (osmotic diuresis) inulin U/P ratios quite uniformly decrease below 8 and approach 1 as a limiting value.

The minimum inulin U/P ratios in the present patients were all below 8 and ranged from 3.4 to 5.9.

Urea/inulin and I^{131}/inulin clearance ratios: In the normal kidney it is believed that approximately 40 per cent of the filtered urea back-diffuses in the proximal segment [*10*]. Presumably this occurs because the proximal reabsorption of water creates a concentration gradient between the urea in the tubular urine and that in the peritubular capillary blood. If water is removed from the urine traversing the distal segment due to the action of antidiuretic hormone, a small additional percentage of urea may back-diffuse. When antidiuretic hormone activity is inhibited, essentially all the urea escaping proximal reabsorption (i.e., approximately 60 per cent of the amount filtered) will be excreted in the urine. However, when proximal tubular water reabsorption is inhibited (e.g., during osmotic diuresis) more than 60 per cent of the filtered urea may be excreted. In each of the three patients in whom appropriate measurements were obtained, over 80 per cent of the filtered urea was excreted.

The mechanisms of the renal excretion of iodide resemble in many respects those for urea [*1*]. At inulin U/P ratios of 8 or greater no more than 50 per cent of the filtered I^{131} is excreted. When U/P ratios fall below 8, however, I^{131}/inulin clearance ratios increase in a manner qualitatively similar to that described for urea. In Case III the mean value for I^{131}/inulin clearance ratios was 61 per cent.

Osmolar clearance: In a normal subject on a normal diet osmolar clearance ranges from 1 to 3 per cent of the filtered water. In experimental osmotic diuresis, however, these values may vary from 10 to 50 per cent. In the three cases in whom measurements were made, maximum values for osmolar clearance ranged from 18 to 28 per cent of the concurrent values for filtered water.

Nature of the Non-reabsorbed Solute. On the basis of the foregoing observations it has been concluded that the polyuria resembled that which is seen in normal subjects during osmotic diuresis.* Since no exogenous loading solute was infused in the present patients, the unreabsorbed solute must therefore have been of endogenous origin.

In the presence of osmotic diuresis induced by infusion of mannitol or urea, the loading substance constitutes approximately two-thirds of the urinary osmols, and electrolytes constitute the remaining third [*11*]. In three of the present patients sufficient observations were available to analyze the solute composition of the urine. In each subject the majority of urinary solutes consisted of electrolytes. Thus in Case I the electrolyte osmolar clearance† constituted 73 per

* Similar values for inulin U/P ratios, urea/inulin clearance ratios and osmolar/inulin clearance ratios may be noted in other renal salt-losing syndromes and in advanced Bright's disease.

† Electrolyte osmolar clearance

$$= \frac{U_{Na}V + U_{Cl}V + U_{K}V}{P_{osm}}$$

where UV = minute rate of excretion and P_{osm} = plasma osmolality. When this calculation was performed using the formula,

$$\text{electrolyte osmolar clearance} = C_{osm} - \frac{U_{urea}V}{P_{osm}} \text{ [11]},$$

comparable values were obtained.

cent of the total osmolar clearance, and sodium and chloride alone constituted 68 per cent of the total osmolar clearance. Although the plasma urea level on the day of study was 70 mg. per cent, the excretion of urea accounted for only 29 per cent of the total solute excreted. In Case II the electrolyte osmolar clearance comprised 52 per cent of the total osmolar clearance, whereas urea constituted only 35 per cent of the total solute excretion. In Case IV, at the height of the diuresis, electrolytes accounted for 72 per cent of the total osmolar clearance.

These data suggest that the unreabsorbed solutes responsible for the diuresis were electrolytes, principally sodium and chloride, rather than endogenous urea or other endogenous osmotically active substances.

Nature of the Defect in Electrolyte Excretion. The occurrence of large urinary losses of sodium and chloride in the presence of decreased glomerular filtration rates and normal or low plasma sodium concentrations can be explained only on the basis of depression of tubular reabsorption of sodium chloride. It is possible to examine the present data for information regarding the site of the predominant abnormality of sodium chloride transport. Inherent in such an analysis is acceptance of the concept that proximal tubular reabsorption of solute and water proceeds in an isosmotic manner.*

During water diuresis, the hypotonic urine may be divided conceptually into two moieties: (1) a fraction which is isosmotic to the plasma; and (2) the remainder which is solute-free water [*13*]. Elaboration of solute-free water is made possible by distal tubular reabsorption of solute (chiefly sodium and an attendant anion) without simultaneous proportional water reabsorption. An approximation of distal solute reabsorption may be made from the amount of solute removed to produce the free water (i.e., the osmotic equivalent of the free water clearance†). During maximal water diuresis this figure equals approximately 13 per cent of the filtered load of solutes. Thus in a normal state about 13 per cent of the filtered sodium is reabsorbed distally and 1 to 2 per cent is excreted.

In Case I, 20 per cent of the filtered sodium was excreted. This figure is greater than could be theoretically accounted for by complete cessation of distal sodium reabsorption. Moreover, that some distal sodium reabsorption occurred, despite the natriuresis, is suggested by the presence of a dilute urine. The amount of solute removed from the urine to achieve the observed degree of hypotonicity was equal to 3 per cent of the filtered load of osmols. In Case II the percentage of filtered sodium excreted was 6.3 per cent. The value for chloride, which is perhaps more satisfactory in that it is not appreciably affected by sodium reabsorbed by cation exchange, was 9.3 per cent. Both of these values could be accounted for by suppression of distal reabsorption. However, the osmotic equivalent of the free water clearance ranged from 9.1 to 12.8 per cent of the filtered load of osmols (average 10.8 per cent). These values which approximate the maximal figure for distal solute reabsorption suggest that, despite the continuing natriuresis and chloruresis, distal reabsorption of sodium and chloride was intact and near-maximal. The lack of osmolality data in Case III precludes calculation of the free water clearance or the osmotic equivalent in this instance. However, the percentage of filtered loads of both sodium and chloride excreted ranged from 12 to 14 per cent. To account for these percentages on the basis of a distal lesion would necessitate the assumption of virtually complete suppression of distal solute reabsorption. The observation that the specific gravity of this patient's urine ranged from 1.010 to 1.010 suggests that he maintained the capacity to elaborate a dilute urine and supplies presumptive evidence that his distal solute reabsorption was not completely suppressed. In Case IV the urine was hypertonic throughout and the possible contribution of distal solute reabsorption could not be calculated.

It is concluded, therefore, that the fundamental lesion responsible for the polyuric state in the cases described was a defect in the tubular transport of sodium and chloride. It is suggested, moreover, that the defect was located predominantly in the proximal segment, and that there was continuing distal solute reabsorption.

Primacy of the Tubular Lesion. In any renal salt and water wasting syndrome, the question must arise as to whether polyuria is due to renal dysfunction or is a homeostatic response to the administration of large volumes of parenteral fluid. In the present patients the observations indicate that polyuria represents, at least in

* Defense of this thesis is beyond the scope of the present discussion but comprehensive reviews may be found in the writings of Smith [*9,12*].

† The calculation of the osmotic equivalent of the free water clearance (T^{d}_{osm}) in μOsm/min. = C_{H_2O} (ml./minute) × plasma osmolality (μOsm/ml.).

part, a failure of the kidneys to defend the integrity of body fluids. The primacy of the renal lesion is especially apparent in Case III in which the polyuric state persisted for over three months despite repeated periods of enforced fluid restriction. There is evidence, however, in Case IV which suggests that the renal excretion of salt and water in a salt-losing state may not be wholly independent of the concurrent fluid intake. In this patient the infusion of an isotonic solution of sodium chloride at the rate of 5 ml./minute during the course of clearance studies evoked a progressive and inordinately large increase in electrolyte and water excretion throughout the periods of observation. Neither the glomerular filtration rate nor plasma sodium concentrations changed appreciably and thus the filtered load presumably remained constant. This exaggerated response to minimal extracellular fluid expansion suggests that the transport mechanisms for sodium and/or chloride were influenced (although in an abnormal manner) by alterations of some function of the extracellular fluid.

Miscellaneous Observations. The explanation for the increase in urea/inulin clearance ratios with falling urine flows (following pitressin in the initial study, Case II) and the decrease in these ratios with rising urine flows (following mannitol infusion in the follow-up study, Case II) is not apparent.

In Case III the response to 10 mg. of DOCA was characterized by a decrease in sodium and chloride excretion rates and in urine flow, and a rise in the percentage of the filtered load of potassium excreted. This is somewhat difficult to reconcile with the fact that prolonged administration of DOCA in amounts up to 15 mg. a day did not decrease the magnitude of polyuria. The possibility that in the acute experiment the parenterally administered DOCA transiently reversed the defect in sodium transport cannot be evaluated on the basis of existing data.

SUMMARY

Observations have been described on four patients in whom an abnormality in renal function developed in association with mechanical obstruction of the urinary tract. Clinically, the presenting manifestations were those of acute renal failure (complete urinary suppression and symptoms and signs of renal insufficiency). Immediately following relief of the obstruction by appropriate instrumentation, polyuria occurred, varying in duration from several days to three and a half months. The maximum twenty-four-hour urine volumes ranged from 4.5 L. to 15 L. and the twenty-four-hour sodium excretion from 250 to 1,900 mEq. Renal function studies were conducted during the diuretic phase in all patients, and in two patients follow-up studies were performed after subsidence of polyuria. The initial studies revealed impairment of glomerular filtration rate, renal plasma flow and concentrating ability. The most impressive feature of the nephropathy, however, was the abnormality in salt and water excretion which was responsible for the polyuria. Analysis of this abnormality, based on current physiologic interpretations, led to the following conclusions: (1) the diuresis was similar to that seen in normal subjects during experimental osmotic diuresis; (2) the diuresis resulted primarily from the delivery into the urine of an excessively high percentage of the sodium and chloride filtered at the glomerulus; (3) the defect in sodium and chloride excretion could be related to suppression of tubular reabsorption; and (4) the latter was located predominantly in the proximal segment. The inability of the patients to decrease salt and water excretion in response to enforced fluid restriction favors the primacy of the tubular defect in the genesis of the polyuria. However, potentiation of the diuresis in one patient by the infusion of an isotonic saline solution suggests that concurrent fluid administration may influence the magnitude of the diuresis.

Follow-up studies demonstrated improvement in the majority of parameters examined, indicating that the nephropathy attendant upon urinary retention includes multiple renal functions.

Certain of the functional patterns noted in the present patients may also be observed in subjects with advanced Bright's disease and with other renal salt and water wasting syndromes. The possibility has been considered, therefore, that qualitatively similar defects in sodium and chloride excretion may be operative in these states.

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Treatment of Renal Failure with the Disposable Artificial Kidney*

Results in Fifty-two Patients

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THE artificial kidney no longer is a last resort and measure of desperation; it has taken its place in the routine treatment of renal insufficiency [1,2]. Its use is indicated whenever temporary relief of uremia offers improvement, but it should be used only as a part of an integrated plan for the treatment of renal failure.

Artificial kidneys remove retention products from the blood and correct imbalance of the plasma electrolytes through the process of dialysis; the small molecules of urea, creatinine, uric acid and other retention products diffuse from the blood through a cellulose membrane into the rinsing fluid; and at the same time the electrolytes in the blood come into equilibrium with those in the rinsing fluid. The advantages of the disposable coil kidney over other artificial kidneys are that it is prefabricated, already sterilized, convenient to set up and easy to operate. It is within reach technically and financially of any medical center where a staff is willing to be trained in the special care required by patients with uremia.

Technique of Dialysis with the Coil Kidney. A coil kidney is taken from storage just before it is to be used. It is flushed with normal saline solution and primed with 750‡ ml. heparinized blood (for a home-made kidney); it is then ready for use. (Figs. 1 and 2.) A kidney with two cellulose tubes in parallel (called a twin-coil kidney) has a dialyzing area of 18,000 sq. cm. One dialysis takes five to six hours.

Blood is withdrawn from the patient through polyvinyl chloride catheters,§ either from the radial artery or via the saphenous vein from the vena cava inferior, and returned to a median cubital, cephalic or jugular vein.

Technical Failures of the Coil Kidney. There has been no leak in any of the coil kidneys manufactured by Travenol Laboratories. One cellophane coil ruptured; insufficient heparin had been used and clotting in the filters occurred; the blood that was being pumped into the artificial kidney caused rupture of the cellophane tubing when the outflow was blocked. This development can be avoided by carefully watching the pressure in the filters (the plastic filter housing can be palpated).

Urea Clearance of the Coil Kidney. The urea clearance of a coil kidney is calculated by using the formula:

$$\text{Urea clearance} = \frac{(B_{\text{inflow}} - B_{\text{outflow}})}{B_{\text{inflow}}} \times \text{flow rate per minute}$$

where B = blood urea.

Since the rinsing fluid is not constantly fresh, a somewhat lower clearance rate may be expected clinically than the 130 to 140 ml. per minute obtained *in vitro.* During clinical dialyses at flow rates of 200 ml. per minute, eleven determinations of the urea clearance of the coil kidney were made; the average clearance was 105 (78 to 133) ml. per minute. Larger blood flows, 200 to 400 ml. per minute, produced larger clearances.

‡ Recently, we have found that 1,100 ml. of blood are necessary to prime the disposable artificial kidney as it is now commercially available.

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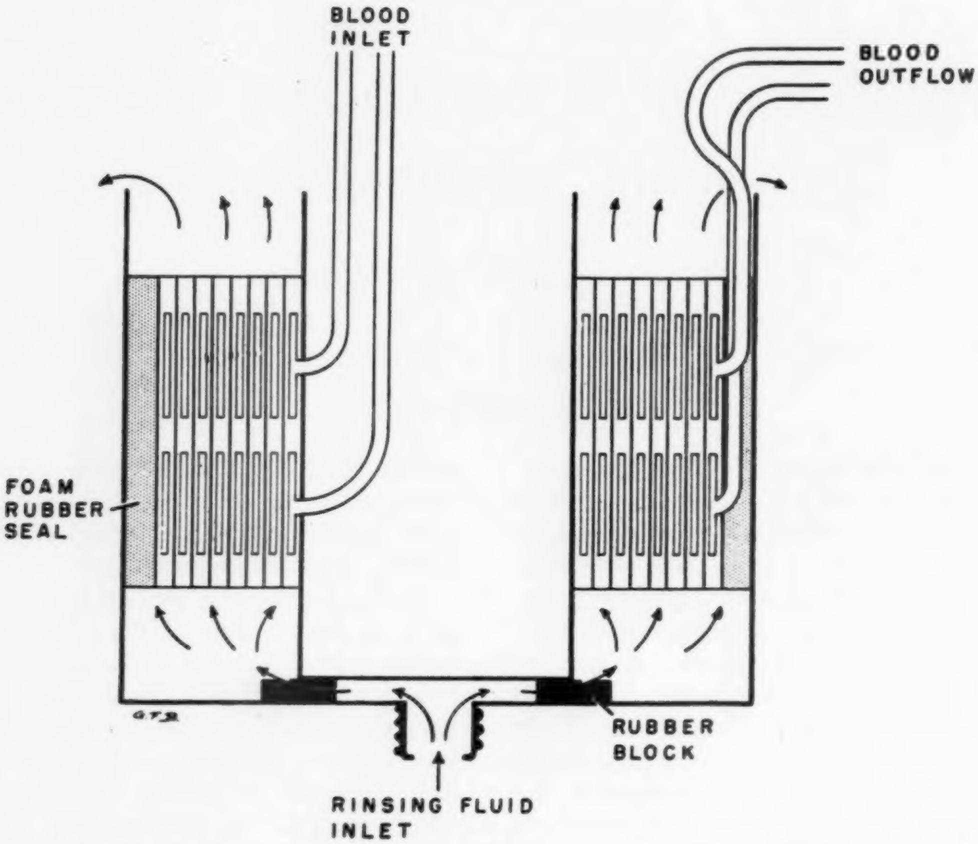

FIG. 1. Diagrammatic cross-section of the artificial kidney in operation. While the blood is pumped through the coils of cellulose tubing, compressed between layers of screen, rinsing fluid is pumped crosswise through the screens. (From: KOLFF, W. J. and WATSCHINGER, B. Further development of coil kidney. *J. Lab. & Clin. Med.*, 47: 969–977, 1956.)

RESULTS

This series comprises the fifty-two patients in whom ninety dialyses were performed during the year 1956. Reported dialyses were performed in twenty-four patients, one of whom was dialyzed eight times.

Acute Uremia. Twenty-nine patients had acute renal failure; fifteen recovered and fourteen died. (Table I.) Of the fifteen patients who recovered, four, including two having anuria following transfusion reactions, might have recovered without benefit of dialysis. However, we believe the remaining eleven patients could not have survived without dialysis, either because of the duration of the anuria or because of the severity of their clinical condition.

In retrospect it would seem that two of the three deaths from crush syndrome might have been avoided. Both patients died in cardiac arrest, one probably from potassium intoxication. Our present experience supports our belief that a second dialysis should be given sooner in these severely ill patients. The third patient died within one minute after an intravenous injection of 60 mg. of heparin.

A patient who had resistant staphylococcal enteritis with sepsis died four days after the first dialysis and at the beginning of the second dialysis when the blood urea was 306 mg. per 100 ml. Although uremia was not the only cause of death, we believe that in that case, too, the interval between dialyses may have been too long. The other patient with resistant staphylococcal sepsis had severe occlusive arteriosclerosis of both legs and his renal function failed to recover. In the other three patients with fatal hepatorenal syndrome, dialysis was performed as a last resort. In one of them, common bile duct stones were overlooked. Although they seemed poor candidates from the start, we believe dialysis was indicated in these patients. To support this belief, we mention a sixty-one year-old man with "hepatorenal syndrome" after prostatectomy whose condition seemed equally hopeless but who recovered after dialysis.

Fig. 2. Close-up of the dialyzing unit, showing the two tubes that carry the blood from the patient to the coil kidney and the two tubes that return the blood to the patient. The rinsing fluid that is being pumped into the dialyzer from the tank flows over the top of the dialyzer and falls back into the tank.

Three patients with overwhelming infection died before any benefit from the treatment could be expected. One had diffuse papillary necrosis of the kidneys and pneumonia with pulmonary edema; one had bronchopneumonia; and the other had sepsis following abortion. The patient who had hyperkalemia after pneumonectomy for tuberculosis died several hours after the dialysis, due to pulmonary insufficiency, although the serum potassium level was corrected to normal.

Fresh, myocardial infarction occurred as a complication in three patients during the period of anuria. We do not see how the occurrence of myocardial infarction could have been avoided.

In summary, of the fourteen patients with acute uremia who died, three might have had a better chance of survival with more frequent dialyses. Of the remaining eleven, in nine life was prolonged and temporary clinical improvement was obtained.

Chronic Uremia. Twenty-three patients had chronic renal failure. Ten died in the hospital and thirteen were clinically improved when they were discharged from the hospital. (Table II.) The results will not be discussed in detail but the following remarks may be useful.

The prognosis of uremia complicated by severe or malignant hypertension was hopeless, and benefit from dialysis, if any, was of short duration, although four of the seven patients could leave the hospital after treatment.

Of three patients with polycystic kidneys, two did very well. One of the latter patients was extremely ill with uremic pericarditis and needed three dialyses, but is now back at work.

The condition of three of four patients with chronic pyelonephritis was improved when they were discharged from the hospital. One patient died thirteen days after the fourth dialysis. However, this patient had had a useful life for six months between the first and the second dialysis.

Dialysis for subacute glomerulonephritis has never been successful in our experience, but in this series the condition of the one patient with this disease, a forty-four year old physician, improved remarkably and his daily urinary output increased to 2 L. after dialysis. However, septic, purulent pericarditis then developed which caused his death.

TABLE I

DATA IN TWENTY-NINE PATIENTS WITH ACUTE RENAL FAILURE TREATED BY DIALYSIS

Category	Total No. of Patients	No. of Patients Recovered	Specific Diagnosis	Duration of Renal Failure Until Urinary Output was 1.5 L./24 hr (days)	No. of Patients Dead	Principal Cause of Death	Duration of Survival After Onset of Renal Failure (days)
Transfusion reaction	3	3	...	11, 9, 11	0	...	...
"Hepatorenal syndrome" Following operation	7	3	Suprapubic prostatectomy (1)	6	4	Occlusive arteriosclerotic disease and staphylococcal sepsis (1)	21
						Cholecystectomy and gastric resection, bleeding duodenal stump (1)	22
Not following operation	..	..	Acute hepatitis (1)	13	..	Common bile duct stone (1)	8
			Meningococcal septicemia (1)	13	..	Carcinoma of prostate and acute myocardial infarction (1)	10
Crush syndrome Following accident	3	2	Retroperitoneal hemorrhage and staphylococcal enteritis (1)	10	1	Crush injury of arms, cardiac arrest (1)	7
			Shotgun wound (1)	3*			
Following aortic grafts	2	..	...	...	2	Cardiac arrest (2)	21, 7
Abortion with hemolytic sepsis	3	2	...	14, 16	1	Overwhelming sepsis	3
Tubular necrosis following major operations (without jaundice)	4	1	Exenteration of pelvis for cancer of sigmoid	12	3	Bronchopneumonia (1)	17
						Staphylococcal enteritis with sepsis (1)	13
						Myocardial infarction (1)	8
Acute diabetic acidosis	2	1	HCO_3^- 5.5 mEq./L.	11	1	HCO_3^- 4.8 mEq./L.; acute myocardial infarction (1)	18
Acute glomerulonephritis	2	2	...	9†, 15†	0	...	...
Miscellaneous	3	1	Bilateral renal stones	6	2	Pulmonary insufficiency after pneumonectomy (1)	10
						Acute necrosis of renal pillae, pulmonary edema with bronchopneumonia (1)	7
Total	29	15	...	Average 10 (Range 3–16)	14	...	Average 12 (Range 3–22)

* This patient was never anuric although severely uremic.
† Urinary output in children never reached 1.5 L. per day.

The duration of clinical improvement is difficult to assess. One patient with carcinoma of the prostate and one with polycystic kidneys are well eight months after dialysis, and their improvement is beyond doubt. The estimated average duration of clinical improvement in the eleven others is seven weeks (two to twenty-four weeks). Actually, the average is higher because some patients were treated recently and are still doing well.

Responses to Treatment. Sedatives are withheld during the first hours of treatment so that any discomfort of the patient may be recognized.

Three patients died during dialysis. Two were near death before dialysis. The third was very ill with fluctuating blood pressure and pericarditis, but his death came unexpectedly after an intravenous injection of ansolysen® (pentolinium bitartrate, 0.9 mg. in three divided doses) given to suppress a rise in blood pressure.

TABLE II

DATA IN TWENTY-THREE PATIENTS WITH CHRONIC RENAL FAILURE TREATED BY DIALYSIS

Diagnosis	Total No. of Patients	Improved Condition When Discharged from Hospital (no. of patients)	Died in Hospital (no. of patients)	Duration of Survival After Last Dialysis in Patients Who Died (days)
Severe or malignant hypertension with or without chronic nephritis	7	4*	3	3, 3, 6
Arteriosclerotic occlusion of renal artery (single kidney)	1	0	1	9
Polycystic kidneys	3	3	0	....
Chronic pyelonephritis	4	3	1	13
Hydronephrosis due to obstructing ureters or bladder neck	3	1	1 (abdominal carcinomatosis) 1 (invasive carcinoma of sigmoid, pericarditis, severe acidosis)	7 Died of cardiac arrest during dialysis
Temporary obstruction of urinary tract, cancer of prostate	2	2	0	....
Chronic glomerulonephritis with chronic and acute pyelonephritis	1	0	1	26†
Subacute glomerulonephritis with purulent pericarditis	1	0	1	24
Necrotizing angiitis	1	0	1	17
Total	23	13	10	Average 11 (Range 3 to 26)

* Three patients returned in cardiac failure and uremia twenty-three, forty-two, or seventy-six days later; the fourth one died at home in cardiac failure and uremia, shortly after discharge from the hospital.

† This patient died twenty-six days after the last dialysis, but fifty-seven days after the first dialysis (Case III).

Stiffness or local pain in the one arm used for cannulation occurred in most patients. Fatigue toward the end of the six-hour procedure was mentioned often by the patients.

The three typical symptoms or signs of uremia, twitching, changes in sensorium and vomiting, when present, usually improved with dialysis; however, fever or severe hypertension sometimes prevented improvement. Generalized twitching occurred in eight of the fifty-two patients before dialysis. In six of these it was lessened or it subsided after dialysis. One patient was comatose and had continuous clonic seizures for five days. These subsided after dialysis; she awoke and began to talk.

Ten of fifty-two patients were mentally clear before dialysis. Forty-two were apprehensive or restless, mentally confused, lethargic or comatose before dialysis; of the patients who lived, only one did not improve.

Nineteen of the fifty-two patients vomited before dialysis. Ten of these nineteen patients vomited during dialysis. Gastric suction was used prior to and throughout dialysis in the nine other patients. Vomiting usually was lessened the day after dialysis; in ten of nineteen patients it definitely diminished. Some patients had good appetites after being dialyzed.

Changes in Arterial Pressure. Arterial pressures were measured every five minutes at the beginning and at least every fifteen minutes during the further course of each dialysis.

TABLE III

CHANGES IN ARTERIAL BLOOD PRESSURE DURING DIALYSIS

		Total No. of Dialyses (90)	Total No. of Patients (52)	No. of Dialysis with Initial Systolic Pressure of 150 mm. Hg or more (38)	No. of Dialyses with Initial Systolic Pressure of less than 150 mm. Hg (52)
Temporary decrease in blood pressure	in systolic pressure >30 mm. Hg	38 (42%)	26 (50%)	19 (50%)	19 (36.5%)
	in diastolic pressure >20 mm. Hg	29 (32%)	22 (42%)	17 (45%)	12 (23%)
Temporary increase in blood pressure	in systolic pressure >20 mm. Hg	40 (44%)	29 (57%)	17 (45%)	23 (44%)
	in diastolic pressure >20 mm. Hg	16 (18%)	14 (27%)	4 (11%)	12 (23%)

A temporary decrease of more than 30 mm. Hg was observed in 50 per cent of the patients with systolic blood pressures of 150 or higher before dialysis, and in 36.5 per cent of the patients with systolic blood pressures lower than 150 before dialysis. (Table III.) The temporary falls in arterial pressure occurred within the first hours of dialysis and rarely caused any concern. The patients did not notice them. Usually the blood pressure could be corrected by a small transfusion of blood. Often 100 ml. of blood was enough; occasionally 300 ml. or rarely 500 ml. was required. In two patients an infusion of norepinephrine (levophed®) also was required.

In six instances the diastolic pressure dropped to below 20 mm. Hg despite maintenance of a normal or high systolic pressure. The fall cannot be attributed to the occurrence of anemia or to the presence of an arteriovenous fistula; the shunt through the artificial kidney is too small. Moreover, when the circulation through the kidney was temporarily shut off, the diastolic pressure remained low. Some patients with acute renal failure had had low diastolic pressure of unknown cause during the course of their disease.

Increases in systolic pressure [*3*] of more than 20 mm. Hg occurred during 44 per cent of the dialyses. (Table III.) Mostly they caused little concern. Sometimes they were most welcome. Five of our patients who were unable to maintain a satisfactorily high blood pressure before dialysis maintained it without further use of pressor agents after dialysis. (Table IV.)

Excessive increases in arterial pressure occurred four times. (Table IV.) In these cases pentolinium bitartrate (ansolysen®) was given intravenously in small divided doses. One patient died during the dialysis after the administration of ansolysen but the death was not necessarily due to the lowering of blood pressure; the patient also had carcinoma of the colon, hydronephrosis, chronic bladder neck obstruction with acute pyelonephritis and pericarditis.

Many patients with acute uremia, and some with chronic uremia, have labile blood pressure. One should be prepared for a fall in blood pressure during the first hours and a rise during the last few hours of dialysis. Both changes are amenable to treatment. The lasting improvement of blood pressure was gratifying in some patients whose hypotension prior to dialysis had resisted all attempts at correction.

Cardiac Irregularities. Cardiac irregularities have not been a serious problem; when they occurred their occurrence was not consistent in the same patient. Temporary auricular fibrillation was noted twice; in each case it reverted to normal sinus rhythm before the following morning. In one patient auricular flutter developed the morning after dialysis. A temporary increase in pulse rate occurred in many patients. Two patients had a transient tachycardia with extrasystoles.

Increases in Temperature. Increases in temperature greater than 1°F. occurred during sixteen of the fifty-two dialyses in which the temperature was recorded. Shaking chills did not occur, but during eight dialyses there was chilliness or a minor chill.

Hemorrhage, Heparin and Clotting Time. Hem-

TABLE IV

DESIRABLE AND UNDESIRABLE RISES IN BLOOD PRESSURE DURING DIALYSIS

No. and Type Patients	Arterial Pressures (mm. Hg)		Results
	Before Dialysis	After Dialysis	
Hypotensive patients (6)	80/49 (60/40–90/50)	117/58 (102/50–142/60)	One patient died; a desirable rise occurred in the five other patients.
			Undesirable Rise Treated with Ansolysen
Patients with normal or high blood pressure (4)	160/100	228/30	1 mg. intravenously; rise controlled.
	164/90	220/110	1 mg. intravenously; rise controlled.
	110/70 (but probably hypotensive before)	200/110	0.25 mg. intravenously; 0.25 mg. intravenously; 0.4 mg. intravenously } patient died.
	210/110	240/100	1.25 mg. intravenously 4 times; rise controlled.

orrhage has been less of a problem than one would expect and even active bleeding has proved to be no contraindication to dialysis.

At the beginning of dialysis, patients were heparinized with 1 mg. of heparin per kilogram of body weight, and 20 or 25 mg. of heparin was added to each bottle of fresh citrated bank blood used for priming the coil kidney or for transfusion. During the dialysis 10 mg. of heparin was given per hour; more was given only when the clotting time was short. The average dose of heparin in adults was 165 mg. (110 to 255 mg.). During the last hour of dialysis no heparin was given.

The clotting time of blood returning from the coil kidney to the patient was determined every hour with Lee-White glass tubes. The beginning of clotting time was interpreted as the time when the blood became adherent to the wall of the tube, even if the clot would not hold when inverted. The clotting time was maintained between fifteen and thirty minutes for the first four hours of treatment. During the last hour, in the thirty-five dialyses in which it was determined, it averaged sixteen minutes (six to thirty minutes). The clotting time was longer than twenty minutes only once.

Some oozing from the cut-down sites occurred in all but three patients. The oozing usually started two or more hours after the onset of dialysis. It was never serious, although gauzes were changed more than ten times in eight patients. Generally, oozing stopped after the wounds had been closed. In twenty-six instances 50 mg. (25 to 200 mg.) of protamine sulfate was given at the end of dialysis. It was immediately effective in all but two patients in whom oozing was then controlled by a pressure bandage.

Minimal hemorrhages have occurred from the rectum, from a nephrostomy wound, from the uterus after dilatation and curettage, from other surgical wounds, from the nose and from the gums. One would expect severe hemorrhages in these cases but they occurred only three times in ninety dialyses. Epistaxis developed once when, against the rules, a catheter for nasal administration of oxygen was applied. One dialysis was started as a life-saving procedure, notwithstanding active bleeding from a duodenal stump; 1,700 ml. of blood was needed to compensate for that lost from hemorrhage. The third patient in this series with severe bleeding was in profound hepatic failure and 300 ml. of blood oozed from the cut-down wound at the saphenous vein.

Postdialysis Decrease of Urinary Output. In fifteen of twenty-nine patients with acute renal failure, diuresis began some time after dialysis; in six there was a slight decrease of urinary output on the day of or on the day following dialysis. (Fig. 3.) In four patients with chronic uremia

there was a pronounced decrease in urinary output following dialysis. For example, a urinary output of 2,000 ml. was temporarily reduced to 850, 1,320 and 1,650 ml. on the day of and on the two days after dialysis, respectively.

An explanation for the phenomenon of relative postdialysis oliguria has been sought by Merrill, Legrain and Hoigne [4] in the reduction of osmotic load. They tried to prevent the decrease by addition of urea to the rinsing fluid. In the patients with chronic renal failure, we have tried to correlate the occurrence of the phenomenon with the change in osmolarity of the blood plasma during dialysis. It seemed that with decrease in osmolarity of more than 5 mOsm./L. during dialysis, urinary output was more likely to decrease after dialysis. Mannitol was sometimes given as an osmotic diuretic with the hope of preventing the postdialysis oliguria. In some patients it seemed to be effective, in others it was not. In one patient with subacute nephritis, urinary output decreased after the first dialysis but increased after the second dialysis when mannitol (37.5 gm.) was given.

Hemolysis. In none of our patients did hemolysis develop as a result of dialysis. One patient with septic abortion had free hemoglobin in the blood at the onset of dialysis. To avoid hemolysis a soft polyvinyl tube* (Tygon or other brand) in the blood pump (Sigmamotor† pump) seems to be better than rubber. Photoelectric determinations of free hemoglobin in plasma confirmed that no significant hemolysis occurred. Initial values ranged from 19 to 37 mg. per 100 ml. Values before and after dialysis differed by an average of only 4 mg. (0 to 10 mg.) per 100 ml. either way.

* Travenol Laboratories, Inc., subsidiary of Baxter Laboratories, Morton Grove, Illinois.

† Sigmamotor, Inc., Middleport, New York.

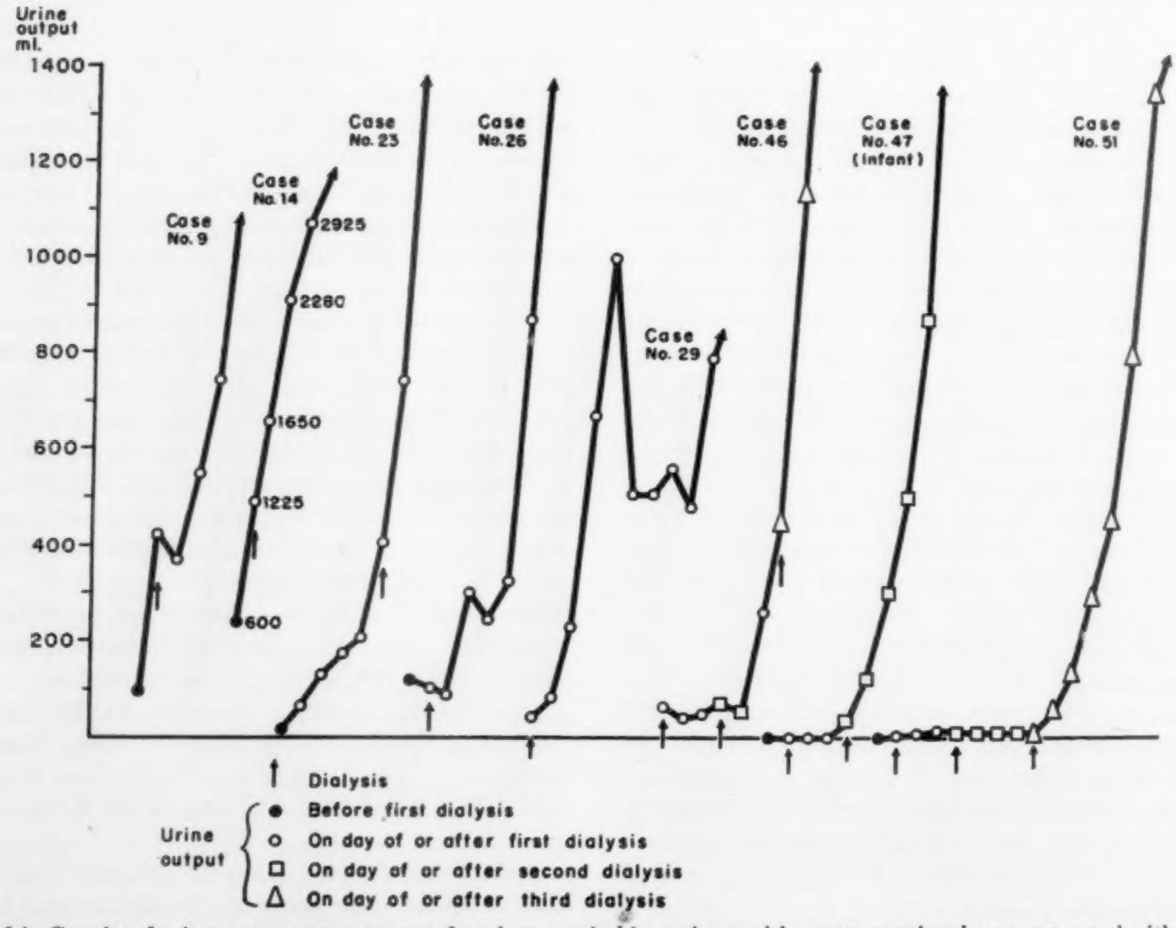

FIG. 3A. Graphs of urinary output per twenty-four-hour period in patients with acute uremia who were treated with the coil kidney. The graph for Case 14 is not based on the scale of the ordinate; urinary volumes (ml.) in this patient far exceeded those in the other patients and are listed specifically. There is no significant decrease in urinary volume in any of the eight patients shown although sometimes there is a short interruption in the upward trend of the lines on the day of dialysis.

PERFORMANCE OF COIL KIDNEY

Urea Removed. Table v indicates the results of dialysis of six hours' duration. The great range is attributable to the wide variations in the initial levels of blood urea and in the weights of the patients. In patients weighing more than 80 kg. a dialysis of six hours' duration suffices to reduce a severe uremia to a mild one; in smaller patients the blood urea may reach normal levels at the end of treatment.

Electrolytes. The composition of the rinsing fluid (Table vi) is adjusted so that in most cases plasma electrolytes are corrected toward normal, although they are not necessarily brought to a normal level. We are reluctant, for example, to increase suddenly a low sodium of 112 mEq./L. to a normal value at the end of the first dialysis. We try, however, to reduce a high serum potassium to a normal level and in order to do that may omit all the potassium from or add only 2.5 mEq./L. to the rinsing fluid of the first bath. The CO_2-combining power, at the end of dialysis or on the following morning, was corrected to an average of 21.5 mEq. Dialysis removes the metabolic acids responsible for acidosis and also provides base, as the rinsing fluid contains 36 mEq./L. of sodium bicarbonate. If the acidosis has been very severe, it may be advisable to administer sodium lactate, for example, 40 mEq./day, during the first day after dialysis. As a result of the correction of the acidosis, Kussmaul respiration, when present, subsided. Plasma chloride is, as a rule, easily corrected.

Ultrafiltration. On the basis of *in vitro* experiments it is assumed that approximately 300 ml. of ultrafiltrate per hour of dialysis is removed from a patient. During treatment, a fall in the patient's weight would be expected. Only nine patients could be weighed before and on the day

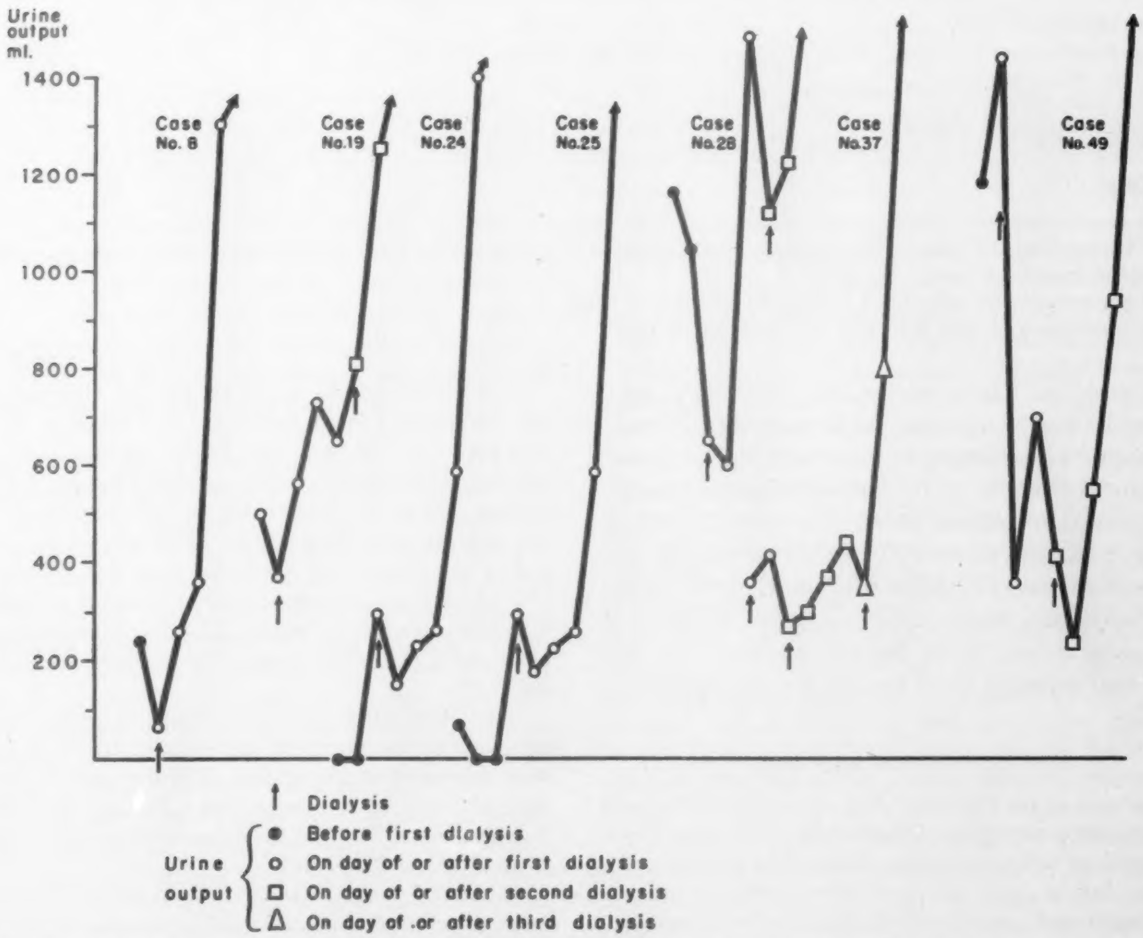

FIG. 3B. Graphs of urinary output per twenty-four-hour period in seven additional patients with acute uremia who were treated with the coil kidney. There was some small decrease in urinary output in six of the seven patients and a larger decrease in one patient.

TABLE V
CHEMICAL RESULTS OF HEMODIALYSIS

	Blood Urea (mg./100 ml.)	Serum Na (mEq./L.)	Serum K (mEq./L.)	CO_2-Combining Power (mEq./L.)	Plasma Cl (mEq./L.)
Number of dialyses	56	60	54	46	32
Before dialysis	228	132	5.3	15.9	85
	(81–542)	(112–148)	(3.7–7.7)	(4.8–35)	(60–102)
After dialysis	101 *	139	4.7	21.5	97
	(36–192)	(125–148)	(3.6–5.85)	14–32)	(87–111)

* Urea removed, mean 93 gm. (39–153 gm.)

TABLE VI
COMPOSITION OF RINSING FLUID* FOR THE ARTIFICIAL KIDNEY

Component	Gm./100 L.	mEq./L.					
		Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO_3^-
Sodium chloride†	570 =	97	..	..	..	97	..
Sodium bicarbonate	300 =	36	..	..	..	...	36
Potassium chloride‡	40 =	...	5	..	..	5	..
Calcium chloride	28 =	...	..	5	..	5	..
Magnesium chloride. $6H_2O$	30 =	...	..	..	3	3	..
Total		133	5	5	3	110	36

* Invert sugar (Travert), 0.4 per cent, and lactic acid to adjust pH to 7.4. During dialysis 10 per cent CO_2 in O_2 is bubbled through to maintain pH.
† Sometimes 600 gm. NaCl (138 mEq. of Na^+) is used.
‡ Sometimes 20 gm. KCl (2.5 mEq. of K^+) is used.

after dialysis. The average loss of weight was 2.5 kg. Ultrafiltration can be increased to 700 ml. per hour by increasing the pressure in the blood outflow line to 250 mm. Hg with a screw clamp.

Removal of edema fluid, without disturbing electrolytes, is considered advantageous in patients with anuria. After dialysis patients often are thirsty and fluid intake has to be restricted if the weight loss is to be maintained. In dehydrated patients fluid can be easily supplied.

TYPICAL CASE REPORTS

CASE I. *Crush Syndrome* (*Fig. 4*): A forty year old man whose abdomen was crushed by a roll of steel was operated on while he was in shock. The kidneys were intact, but a large retroperitoneal hematoma was evacuated and a small rent in the superior mesenteric artery was repaired. The patient was given 14 pints of blood. Oliguria ensued and he became mentally confused. Pitting edema developed over the sacral region.

Five days after the accident he was transferred to the Cleveland Clinic Hospital. The blood urea was 276 mg. per 100 ml. The serum sodium was 135; serum potassium, 5.7; CO_2 combining power, 4.8; and plasma chloride, 104 mEq./L. The patient was dialyzed as soon as possible. After six hours, at the end of the treatment, the blood urea was 99 mg. per 100 ml.; the serum sodium was 139; serum potassium, 4.2; CO_2 combining power, 22; and plasma chloride, 103 mEq./L. The patient's general condition improved.

Four days after the first dialysis the patient was again mentally confused and even violent; his condition appeared to be critical. The day after a second dialysis the urinary output was 1,240 ml. per twenty-four hours; thereafter, daily urinary output ranged from 2,000 to 3,000 ml.

While the patient was in the hospital two complications developed: a wound disruption and staphylococcal enterocolitis. Two months after the accident he was discharged in good condition with normal blood urea.

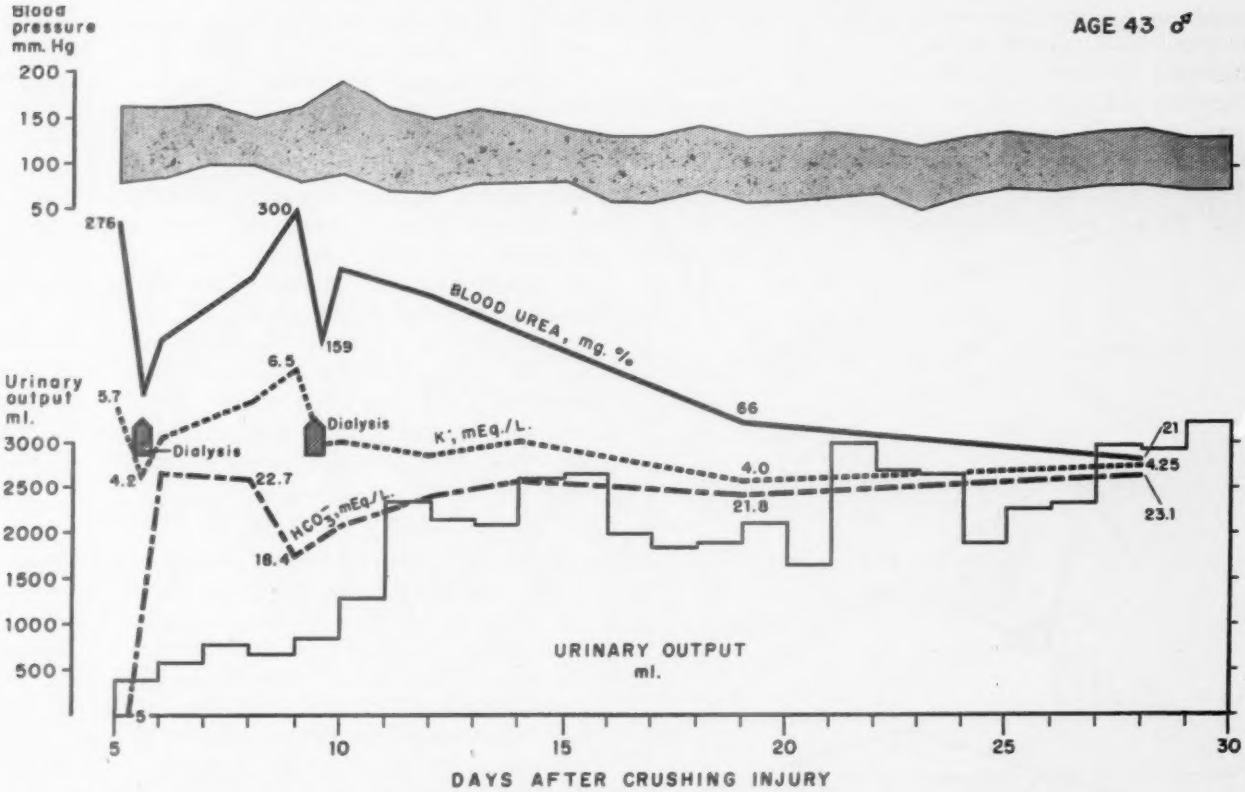

FIG. 4. Case I. A man with crush syndrome and oliguria. The rapid initial increase of blood urea and serum potassium was attributed to breakdown of proteins, probably from blood extravasation. A urinary output of 800 ml. per twenty-four hours was not sufficient to prevent the development of uremia in this patient. Each of two dialyses improved his clinical condition dramatically.

Comment: In this patient, there was clinical improvement after each dialysis. Susceptibility to infection with organisms resistant to the common antibiotics often is seen in patients with uremia. The delay in wound healing suggests that surgical sutures should be left in place longer than usual.

CASE II. *Anuria Following Operation* (*Fig. 5*): The patient was a sixty-one year old woman who had been operated on for adenocarcinoma of the rectosigmoid junction. Radical operation with exenteration of the pelvis was performed and the ureters were transplanted into an ileal pouch. After operation oliguria developed; the urinary output was less than 140 ml. per day, and uremia resulted. After five days of oliguria the blood urea rose to 81 mg. and the plasma creatinine to 5.4 mg. per 100 ml.; the CO_2 combining power fell to 17 mEq./L. She was very weak and hope of recovery was given up.

She was then treated with the coil kidney for six hours. Her clinical condition improved, and the urinary output gradually increased to 1,930 ml. Blood values obtained six days after dialysis were normal except for a CO_2 combining power of 17 mEq./L. After a difficult thirty-three day convalescence she was discharged from the hospital in good condition. The urinary pouch was functioning satisfactorily.

CASE III. *Patient with Anuria, Maintained for Sixty-three Days* (*Fig. 6*): A fifty-seven year old housewife had her appendix removed because of pain in the right side of the abdomen. In retrospect she must have had pyelonephritis. After the operation oliguria developed leading to anuria, and the patient rapidly became hypertensive and disoriented. Twitching developed and gradually increased in severity, culminating in generalized convulsions. At the time of her arrival at the Cleveland Clinic Hospital on the fifth day after the operation, she was cyanotic and unable to speak. The blood urea was 282 mg. per 100 ml., the CO_2-combining power was 10 mEq./L.

She was immediately treated with the artificial kidney. After dialysis it was easy to suppress the twitching with a small dose of amytal® sodium (amobarbital sodium), which had not been effective before. Convulsions did not recur during the stay in the hospital. Diuresis never was restored; the largest output of urine was 45 ml. per twenty-four hours. She could be kept in tolerable clinical condition by dialysis every three days, but whenever the interval was increased to four days or longer the clinical symptoms of uremia increased in severity. The blood urea never was allowed to climb over 180 mg. per 100 ml., and the plasma creatinine was maintained at a level of about 5 mg. per 100 ml. The patient's

condition was tolerable but not good. She was unable to retain food most of the time, and she deteriorated mentally. This may have been due in part to a spiking fever derived from the pyelonephritis, for which a wide variety of antibiotics had been given, and to the severe hypertension that occasionally necessitated administration of a ganglionic-blocking agent (2.5 mg. ansolysen intramuscularly). The blood pressure gradually returned to normal levels. After the eighth dialysis hope was abandoned and dialysis was not repeated; she died twenty-six days after the last dialysis, on the sixty-third day after the onset of recognized renal failure. Necropsy revealed chronic glomerulonephritis and superimposed acute necrotizing pyelonephritis of the right kidney. Nearly all glomeruli were destroyed. No damage of the arteriolar walls could be detected in any organ.

Comment: The course in this patient proves that life can be maintained for sixty-three days with the artificial kidney in the virtual absence of renal excretory function. There is no reason to doubt that life could have been further prolonged had dialysis been continued.

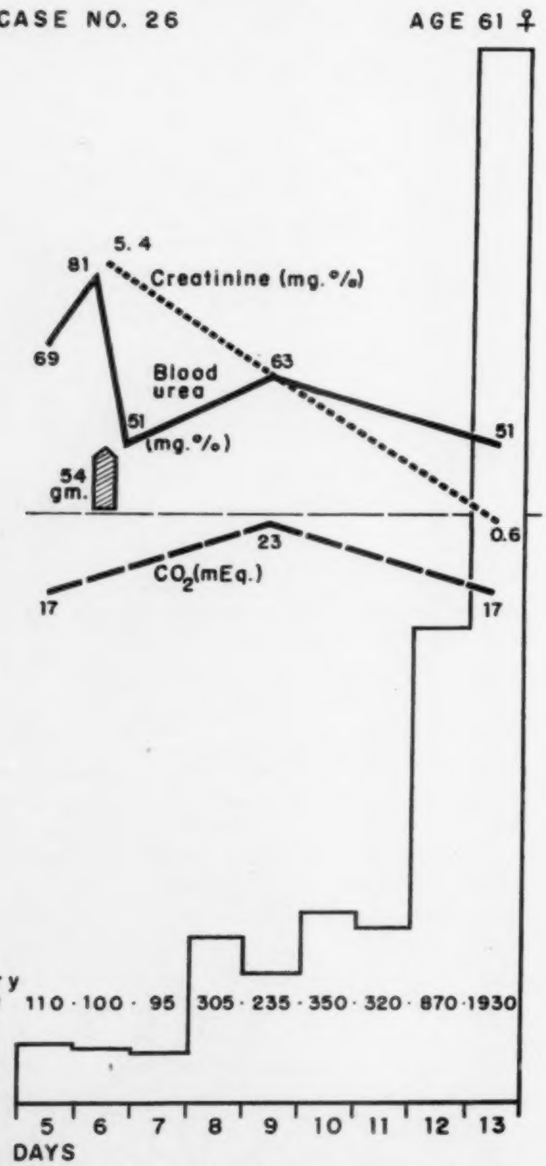

Fig. 5. Case II. A sixty-one year old woman who became oliguric and uremic after abdominoperineal sigmoid resection. The patient's starvation diet for a considerable time before dialysis accounts for the slight increase in blood urea during the period of oliguria. The relatively low blood urea of 81 mg. per 100 ml. does not at all reflect the clinical seriousness of this patient's condition. Her clinical condition did not improve and, because of an unpredictable loss of drainage fluid from large raw surfaces, it was difficult to maintain balance of electrolytes. After one dialysis her clinical condition rapidly improved. This result supports the present trend to give a patient the benefit of dialysis before threatening blood chemical changes develop.

Case IV. *Chronic Uremia Temporarily Improved:* Acute pyelonephritis developed in a thirty-seven year old man in 1945. He worked regularly as a clerk until November 1955, when he was first hospitalized for anemia, edema of the feet and renal failure. The blood urea was 219; uric acid, 9.6; creatinine, 11.4 mg. per 100 ml.; the CO_2 combining power was 10; chloride, 107; sodium, 138; potassium, 4.8 mEq./L. The daily urinary output ranged from 1,000 to 2,000 ml. Since a medical regimen including a high-caloric, low-protein diet failed to improve the condition, the patient was treated with the coil kidney on February 8, 1956. The blood urea level was lowered to 102 mg. per 100 ml. He gained in appetite and strength, and the urinary output increased to more than 2,000 ml. per day. He was discharged three days after the dialysis, with instructions to follow a high-caloric, low-protein diet, moderately restricted as to sodium, with ediol® (fat emulsion) 30 ml. three times daily and one 30 mEq. dose of sodium lactate daily. Except for two short periods of hospitalization for blood transfusions, the patient worked regularly for six months until August 20, 1956. At that time, chills, fever and pericarditis developed. He became oliguric and severely anemic.

The patient was treated three more times with the artificial kidney, each time with excellent clinical results. Although vomiting was lessened and the patient felt much better, renal function did not recover. He died thirteen days after the fourth dialysis.

Necropsy report: Fibrinous pericarditis and severe chronic pyelonephritis (most of glomeruli were completely hyalinized and the corresponding tubules showed severe atrophic changes).

Comment: The course in this patient shows the possibility of temporary improvement and of a "new start" in the treatment of patients with chronic uremia, but it also shows the ultimate futility of all measures when damage to the kidneys is irreversible and the amount of remaining functioning renal tissue is too small to maintain life.

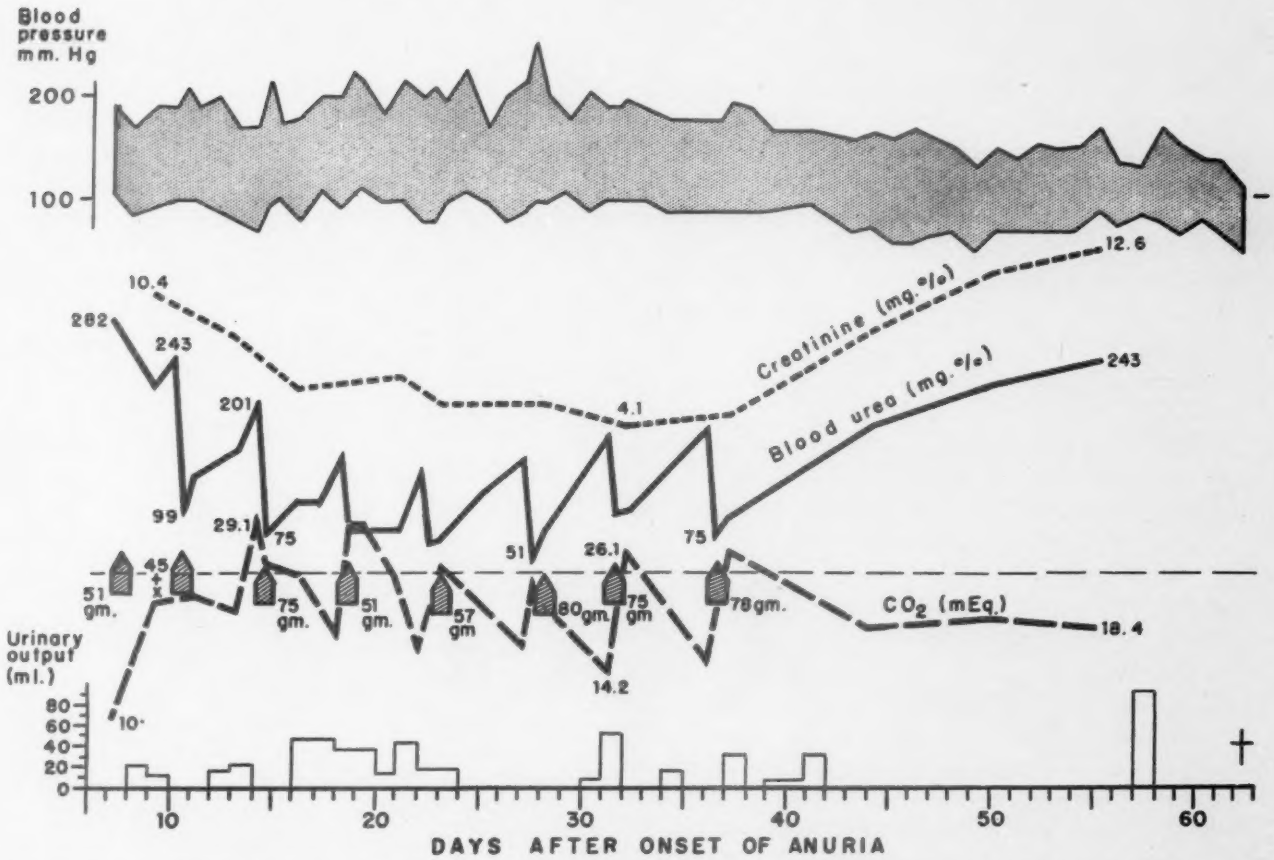

FIG. 6. Case III. This fifty-seven year old woman was maintained for sixty-three days of virtual anuria, thus demonstrating that the artificial kidney can replace renal excretory function. Convulsions stopped and did not recur after the first dialysis. The blood pressure, which at first was high, gradually returned to normal levels. Note the slower increase in blood urea during the latter course of anuria as the patient was gradually entering a chronic stage. Also note that with each dialysis the HCO_3^- was improved.

SUMMARY

The results of treatment with the coil (disposable artificial) kidney in ninety dialyses in fifty-two patients described in this paper establish this type of artificial kidney as a useful tool for the treatment of uremia. The prefabricated coil kidney is more convenient to set up and easier to use than any other type of artificial kidney yet devised, and is now commercially available.

Of twenty-nine patients with acute renal failure, fifteen recovered. Three more might have survived if the present concept of earlier dialysis had been fully applied to them. We now believe that a patient with severe trauma, crushing injury, fulminant infection or intoxication should be given the benefit of dialysis before chemical changes in the blood indicate impending danger. Such a patient may have to be dialyzed every two or three days.

Of twenty-three patients with chronic renal failure, thirteen were in improved condition when they were discharged from the hospital.

Among the symptoms and signs of uremia that improved during or after dialysis were twitching, convulsions, disturbances in sensorium, vomiting and Kussmaul respiration. Changes in blood pressure during dialysis could not always be avoided. Decreases in blood pressure, when they occurred, were controlled by transfusion of small amounts of blood. Increases in blood pressure, when they occurred, sometimes required the administration of a ganglionic-blocking agent. In five of six patients with intractable hypotension before dialysis, the increase in arterial pressure during dialysis was beneficial and could be maintained.

Hemorrhages due to heparin caused no serious problems in this series. (Nasal administration of oxygen and manipulation of other tubes through the nose should be avoided.) Electrolytes were corrected in a manner that could be predetermined by the composition of the rinsing

fluid; the use of standardized rinsing fluids proved satisfactory.

Urea clearance rates were determined during eleven dialyses at flow rates of 200 ml. per minute. The average clearance of 105 ml. per minute was lower than that found experimentally (130 to 140 ml. per minute). Larger blood flows, up to 340 ml. per minute, have recently been used, with an increase in clearance After dialysis a decrease of urinary output was insignificant in the patients with acute uremia but was pronounced in some of the patients with chronic uremia.

The rate of ultrafiltration with the coil kidney approximates 300 ml. per hour of dialysis but it can be increased to 700 ml. Ultrafiltration is considered advantageous as most patients with uremia are edematous.

Four typical case reports are presented: (1) A man in acute uremia due to crush syndrome, whose clinical condition improved after dialysis. (2) A woman with anuria following an extensive abdominoperineal operation in whom early dialysis facilitated management. (3) A woman who was maintained for sixty-three days of virtual anuria; the course in this patient proves that the artificial kidney can replace excretory renal function amazingly well. (4) A man with chronic uremia who after a single dialysis was restored to useful life for six months. The course in this patient demonstrates the possibility of worthwhile temporary improvement with one dialysis, but it also demonstrates the ultimate impotence of all measures in chronic renal disease.

Acknowledgments: The authors gratefully acknowledge the technical assistance of Mr. Janis Eglajs and Miss Rose Litturi.

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Characteristics of Leukocytes in the Urine Sediment in Pyelonephritis*

Correlation with Renal Biopsies

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The identification of persons with significant infections of the urinary tract in the absence of acute symptoms and prior to the development of renal insufficiency is a difficult and important clinical problem. It is likely that the most important clues in this respect will be found in the urine, despite the statement of Thomas Fuller, ". . . reasons drawn from the urine alone are as rigid as the urinal" [*1*]. It is likely also that the most reliable evidence of significant infection is the inflammatory response of the host.

In 1951 Sternheimer and Malbin [*2*] reported on the clinical recognition of pyelonephritis by means of a new stain for urinary sediment. Through the application of this staining technic the authors found a correlation between the occurrence of pale-staining, vacuolated leukocytes that showed random (Brownian) movement of their cytoplasmic granules and the presence of advanced pyelonephritis. These leukocytes occurring in the urine have become known as "granular motility cells" or "glitter cells." The histologic proof of pyelonephritis in the investigation noted was obtained from autopsies, and although the correlation was valid it was necessarily limited to patients who had suffered from advanced renal disease and who had had impaired renal function during the period of clinical study. It would obviously be important to be able to diagnose renal infection before it was so far advanced.

The present studies concern the characteristics of leukocytes in the stained wet urine sediment of persons with infected urine and correlation of the findings with the histology of the kidney in specimens obtained from the patients by percutaneous renal biopsy. Three distinct morphologic types of leukocytes were observed in the urine. Active renal parenchymal inflammation was accompanied by urine sediments that contained two varieties of leukocytes which differed only by the presence of Brownian movement of the cytoplasmic granules.

MATERIAL AND METHODS

The urine specimens were obtained from female patients by sterile catheterization. Samples of voided urine were collected from men after careful cleansing of the urethral meatus. Fifteen ml. of the urine were centrifuged and the packed sediment resuspended in 0.5 ml. of the supernatant urine. Two or three drops of the safranine and gentian violet stain described by Sternheimer and Malbin [*2*] were added and the sediment placed under a cover slip on a clean glass slide. The preparation was examined immediately. All the urinalyses were performed by one of us or a single technician trained in the technic

The procedure for renal biopsy and the methods of bacteriologic and histologic study have been reported previously [*3,4*]. The pathologic diagnosis was made in cooperation with Dr. Frederick Dallenbach of the Department of Pathology by independent examination of the fixed sections stained with hematoxylin and eosin. The histologic abnormalities evaluated in arriving at the diagnosis of pyelonephritis were leukocytes or "colloid" in the tubules, infiltration of the interstitial tissues with inflammatory cells, invasive glomerulitis, interstitial and periglomerular fibrosis and the general microscopic architecture of the kidney. Other coexisting pathologic lesions were always noted when they were present.

All the patients were admitted to the hospital for study and for renal biopsy; their observation was continued in the outpatient department. Infected urine was the only characteristic in common among the patients from whom a renal biopsy was obtained. Some patients had no symptoms of urinary tract infection; a few had recent episodes of clinical acute pyelonephritis, and most patients had had chronic or

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recurrent symptoms related to the urinary tract. Urinalyses were performed in other patients for purposes of comparison, and some hospital patients were examined in order to obtain pus from wounds and blood for a comparative study of leukocytes.

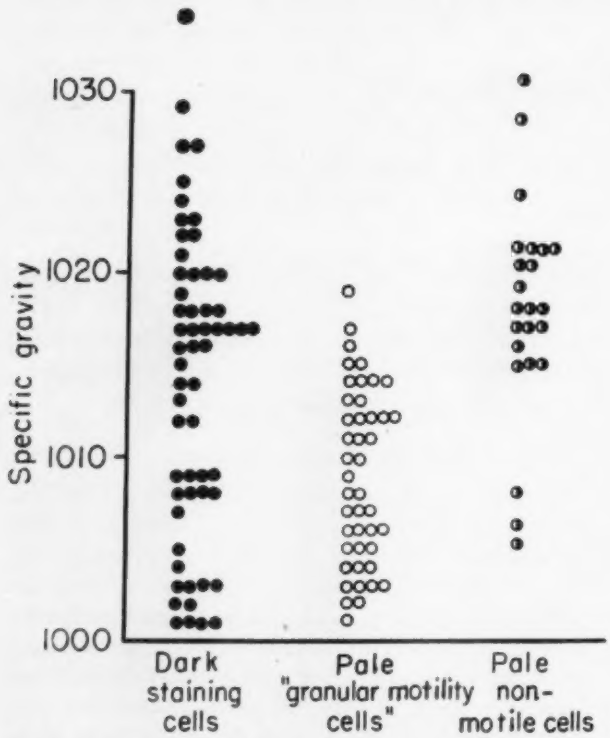

Fig. 1. Morphology of leukocytes in urines of different specific gravity (124 urinalyses from seventy-one patients with pyuria).

RESULTS

Properties of Leukocytes in the Urine. Polymorphonuclear leukocytes in the urine sediment were observed with regard to their size, staining characteristics and the presence of motility of their cytoplasmic granules. Upon the basis of their staining properties two distinct varieties of granulocytes could be recognized, as follows: (1) A dark-staining cell the nucleus of which was a reddish purple and the cytoplasm which was colorless to pink. The cytoplasmic granules in this type of cell were fairly coarse and never showed motility. (2) A pale-staining cell the nucleus of which was colorless or pale blue, less distinct than in the previously mentioned cell, and the cytoplasm was colorless or a faint blue with fine granules. The larger size of this cell and of its nucleus gave it a swollen appearance in some urine specimens.

Motility of the cytoplasmic granules occurred only in pale cells. When fully developed it was a striking phenomenon, and the rapid random movement gave the cell a glittering appearance. When cells from many different urine sediments were examined great variation in the intensity of the motion was observed. In some specimens all the pale cells uniformly showed

Fig. 2. Microscopic characteristics of leukocytes in urine.

vigorous granular movement; in other specimens the motion was slower and less obvious, or could be seen only faintly in a few cells; occasionally it was limited to a focal area in the cytoplasm; and finally, in a number of specimens no granular motility at all could be detected in the pale-staining cells. Throughout the entire scale of transition from motility to non-motility, the staining characteristics of the pale cells remained essentially unchanged and always distinct from those of the dark-staining cells. The pale granulocytes with non-motile granules were slightly smaller than those with granular motility. Commonly, both dark- and pale-staining cells were observed in the same urine specimen.

Leukocyte Properties and Specific Gravity. For purposes of analysis, pale cells with granular motility, regardless of the degree, were distinguished from pale cells with non-motile granules and from dark-staining cells. Figure 1 illustrates the occurrence of granulocytes with the foregoing three characteristics observed in 124 urine samples, in relation to the specific gravity of the urine. Dark-staining leukocytes occurred in urines with various specific gravities within the physiologic range. Granular motility in pale-staining cells was observed only in urine specimens with a specific gravity of 1.019 and less. With few exceptions, the pale cells with the

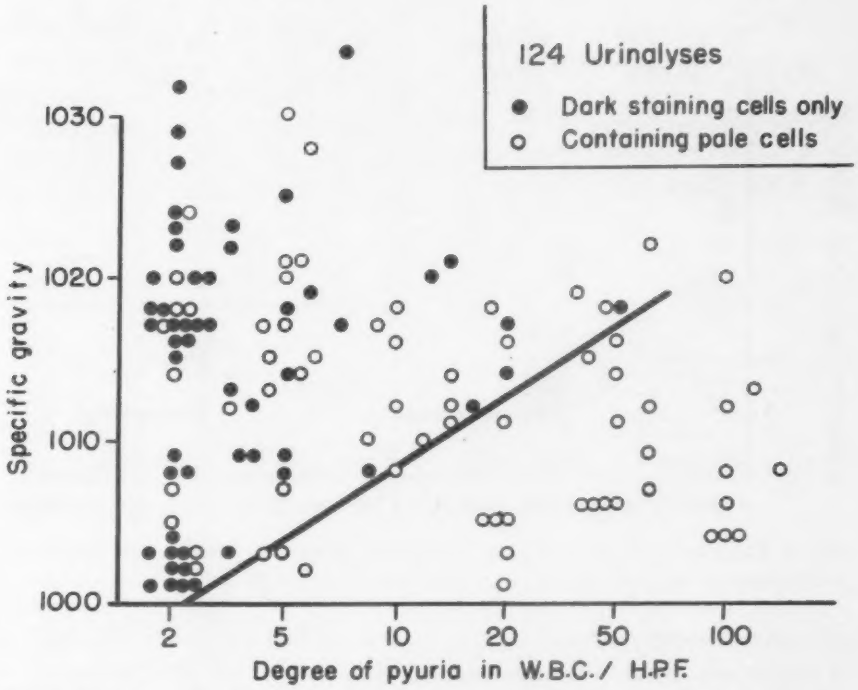

FIG. 3. Staining of leukocytes in relation to the degree of pyuria and the concentration of the urine.

non-motile granules occurred when the specific gravity of the urine was 1.015 or higher.

That differences in the relative concentration of electrolytes and crystalloids in the medium were determining factors for granular motility was supported by adding enough sodium chloride to a sample of urine to raise the specific gravity to 1.022. The initial specimen, which had a specific gravity of 1.007, contained pale leukocytes with vigorous granular motion. After the specific gravity was increased the sediment was stained and no granular motility was observed, although the pale-staining properties of the cells remained. Another aliquot of this urine was centrifuged and the sediment was resuspended in a solution of potassium chloride with a specific gravity of 1.008. No granular motility was present after staining the cells sedimented from this preparation even though the specific gravity approximated that of the natural urine. To another sample glucose was added until the specific gravity was 1.024. Granular motion was diminished but still present. In none of these preparations were the staining characteristics of either dark or pale cells significantly altered, and the ratio of the two types remained nearly constant. Figure 2 schematically summarizes the foregoing features.

Clinical Observations. The urine sediments obtained from patients with pyuria contained either both pale- and dark-staining granulocytes of varying ratio to one another, or only dark-staining cells. Sediments with only pale cells were uncommon.

Because motility of the cytoplasmic granules was dependent upon the composition of the urine the staining characteristics of the leukocytes were considered more meaningful in the early stages of renal disease. To evaluate the significance of the pale cells they were considered as a single group, whether or not the granules were motile, and dark-staining cells were disregarded when pale cells were present in the same specimen.

In Figure 3 the staining properties of the leukocytes and the specific gravity of the urine in which they occurred are plotted with respect to the magnitude of the pyuria. The number and distribution of pale cells were random with regard to the specific gravity of the urine. With high degrees of pyuria, pale cells were almost invariably present regardless of the specific gravity of the urine. This suggested a relationship of pale cells to inflammation which was independent of the rate of urine flow. On the other hand, the maximum number of dark-staining cells was limited in a linear fashion by the concentration or dilution of the urine, which suggested a dependence upon the rate of urine excretion since the staining characteristics of

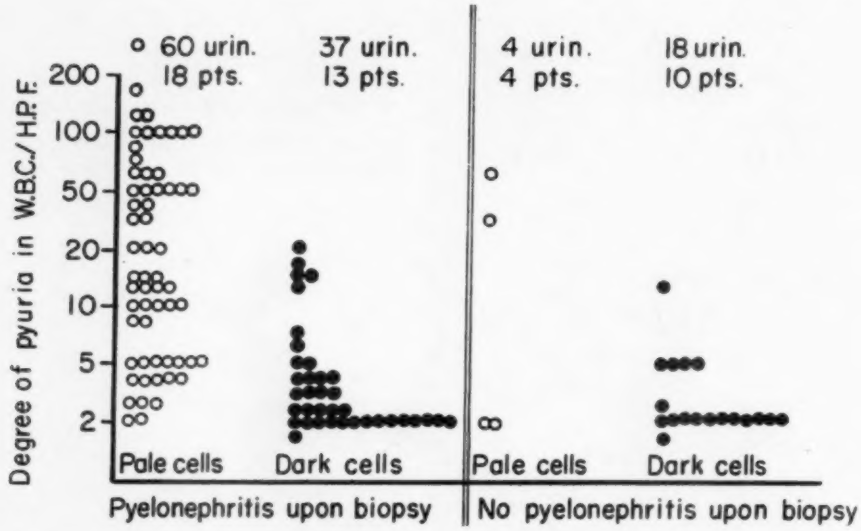

FIG. 4. Correlation of biopsy data and pyuria among twenty-one patients with pyelonephritis and eleven patients with normal kidneys.

the leukocytes were not materially altered by the specific gravity of the urine. In urines with low degrees of pyuria many of the pale-staining cells were of the type without granular motility. (Table I.)

TABLE I
LEUKOCYTE CHARACTERISTICS WITH VARIABLE DEGREES OF PYURIA

Data	Degree of Pyuria (no. white blood cells per high power field)		
	<10	10–50	>50
Number of urinalyses	78	33	13
Number with pale cells	28	26	13
Per cent with pale cells	36	79	100
Per cent pale cells with non-motile granules	47	27	15

Pale Cell Pyuria and Pyelonephritis. The staining characteristics of urinary leukocytes and the findings in the biopsy specimens are shown in Figure 4. The 119 urinalyses shown in this graph stem from thirty-two patients, all of whom had one or more renal biopsies. The data are arranged in pairs of columns correlating the pale cells in the urine sediment with the presence of pyelonephritis in biopsy specimens. The term "pyelonephritis" indicates all stages of classic pyelonephritis as well as evidence of infection of the renal parenchyma associated with renal disease of other etiologies.

Among the thirty-two patients from whom biopsy specimens of the kidney were obtained, an unquestionable diagnosis of pyelonephritis was made in twenty-one. The biopsy specimens from eleven patients were normal or the changes were insufficient to warrant the diagnosis of pyelonephritis. On the average, twice as many urinalyses were performed in the group with pyelonephritis.

The data indicate that all degrees of pyuria may occur in the presence of active chronic pyelonephritis. Massive pyuria, 30 white blood cells per high power field or more, was observed only in conjunction with pyelonephritis, but it was encountered on the average in only one of four urinalyses from these patients. With low degrees of pyuria, pale cells were not invariably present; however, ten of thirteen patients with pyelonephritis established by biopsy, who were observed to have only dark-staining cells in one urine specimen, exhibited pale cells in other urine specimens. The remaining three had only a single urine examination.

Among eleven patients without evidence of pyelonephritis in the biopsy specimens (columns 3 and 4, Figure 4), the urine sediment contained only dark-staining cells, with the exception of four urine specimens from four patients. It is remarkable, however, that in all four of these patients there was clinical evidence of renal infection. In one case a febrile illness with massive pyuria had occurred one month prior to the biopsy; in another patient there was a deformity

of the calyceal system localized to the upper pole of one kidney as demonstrated by a roentgenographic pyelogram. The remaining two patients with minimal pale cell pyuria (2 white blood cells per high power field) at the time of observation had a history of urinary symptoms

TABLE II
PER CENT PALE-STAINING LEUKOCYTES

Hours of Incubation	Blood, Direct to Salt Solution	Venous Blood, Heparinized	Pooled Buffy Coats from Oxalated Blood	Pus from Infected Fistula
0	92	89	36	55
24	83	61	18	37
48	..	..	1	..
72	..	..	..	22

and repeated genitourinary instrumentation extending over more than three years. In both these biopsy specimens minor abnormalities were noted. Thus making allowance for the possibility of unrepresentative biopsies, pale cells were found in the urine of twenty-two patients, eighteen of whom were proved by biopsy to have pyelonephritis and four of whom had clinical evidence but no histologic proof of the disease. Seven patients without pyelonephritis did not have pale leukocytes in the urine.

Successful renal biopsy invariably was followed by a short episode of hematuria of varying degree; therefore urinalyses performed after biopsy were not tabulated in the aforementioned diagram. Granulocytes that were conveyed from the blood stream into the urine by trauma to the kidney were found to be of the pale-staining variety regardless of the histologic renal diagnosis.

Comparison of Leukocytes in Urine, Blood and Pus. The supravital staining characteristics of leukocytes in the blood stream were observed for comparison. Venous blood added to isotonic Hank's balanced salt solution immediately after aspiration and then supravitally stained contained 92 per cent pale-staining granulocytes and 8 per cent dark cells. Leukocytes from the buffy coat of venous blood which was collected and centrifuged in siliconized glassware and resuspended in balanced salt solution showed 89 per cent pale cells and 11 per cent dark-staining leukocytes. The buffy coats aspirated from 15 to 20 hematocrit tubes prepared from venous blood drawn into "double oxalate" were pooled and examined in the same manner. Under these conditions only 26 per cent of the granulocytes were pale, 74 per cent were dark-staining.

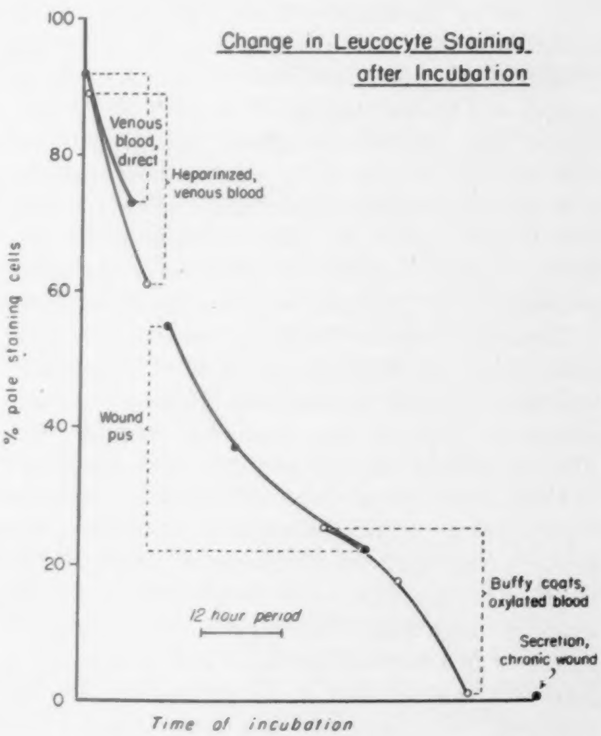

FIG. 5.

The supravital staining properties of fresh pus obtained from an infected fistula caused by a foreign body was observed to consist of 55 per cent pale cells and 45 per cent dark cells. All the granulocytes were found to be of the dark-staining variety in secretion expressed from the closed stump of an amputated limb that was not inflamed.

In Vitro Changes in Leukocyte Staining. Leukocytes that were present in fresh and oxalated blood and those found in pus from an inflamed wound were suspended in balanced salt solution and stored in a refrigerator. The percentage of pale-staining cells decreased uniformly in all the specimens, with a corresponding increase in dark-staining cells, as shown in Table II.

The data from Table II can be represented by a curve, as shown in Figure 5, which illustrates the observed transition of pale into dark-staining cells. Lysis of pale cells did not appear to account for the increased proportion of dark cells.

Rather the transition appeared to be a true one and it was considered to be related to the process of aging.

COMMENTS

Brownian movement of the cytoplasmic granules in polymorphonuclear leukocytes was observed by dark field microscopy in 1908, and in the following year it was correlated with the presence of pyelonephritis or renal abscess as opposed to the findings in cystitis [*5*]. Sternheimer and Malbin [*2*] described the granular motility cell as well as a smaller blue-staining cell with non-motile granules. Their clinical correlation, however, was made only for the former type cell which was observed in the urine sediment of all patients who had pyelonephritis at autopsy. Further observations indicated the importance of the composition of the urine, especially osmotic factors, in producing the characteristics seen in the granular motility cell. The conclusion was reached that the appearance of these cells in the urine invariably denoted a combination of an inflammatory process in the urinary tract with renal functional damage. The sediment stain has been employed in several investigations since that report, but because of the prior orientation attention was given only to cells with granular motility, and only this criterion was accepted as an indication of pyelonephritis.

Almost no emphasis has been placed upon the significance of the differential staining characteristics of urinary pus cells irrespective of granular motility, although this was suggested also by Berman et al. [*6*], and the gradual transition from granular motility to non-motility in the pale-staining cells has not been described. The fact that a single urine specimen often contains pus cells of both the dark-staining and the pale blue-staining variety simultaneously indicates that the staining characteristics of individual granulocytes are, at least in part, independent of the medium. This was corroborated by laboratory observations. Granular motility, on the other hand, was altered by changes in the suspension medium *in vitro;* and in urine the phenomenon was observed only in specimens within the lower range of specific gravities. Clinical experience further showed that consecutive urine specimens taken from the same patient might alternately contain motile and non-motile pale-staining granulocytes.

Other workers have observed that the critical osmolarity for granular motility is approximately 600 mOsm./L. and motility can be inhibited by higher concentrations [*6*]. Osmolarity is only crudely reflected by specific gravity of the urine but nevertheless the specific gravity of the urine served to establish the correlation with granular motility observed in our data. That the total osmolarity is not an isolated single factor in determining granular motility can be concluded from the variation among different solutes in their power to inhibit motility. Electrolytes particularly differ in this regard, and it is likely that the intracellular ionic concentration and equilibrium gradients across the cell membrane are determining factors in respect to the motion of cytoplasmic granules. Decreased viscosity of the cytoplasm might be the net effect of the factors that induce motion [*7*].

Consideration of the two factors suggests to us that the staining behavior of the cells is the more significant criterion for distinguishing two different entities among the granulocytes in the urine. Motility of the cytoplasmic granules is a variable characteristic which reflects only certain properties of the suspension medium. Therefore we consider that the finding of pale-staining cells, without regard to the pressure or absence of granular motility, is more significant than the presence of granular motility cells.

The pale-staining leukocyte has been considered a degenerative form of granulocyte derived from the blood [*2,8*]. Data presented here suggest that actually it is a younger cell than the dark-staining leukocyte and indeed it might be quite representative of circulating leukocytes. Approximately 90 per cent of the granulocytes in freshly drawn blood had similar pale-staining characteristics as did also those in the urine sediment during microhematuria. The ageing of leukocytes, from blood, pus or urine, in isotonic balanced salt solution resulted in a progressive change to dark-staining cells.

Observations on incubated pus cells were reported as early as 1925 by Seyderhelm [*9*] who used a supravital stain consisting of Congo red and trypan blue. The findings were interpreted as showing that aged cells allowed the colloidal stain to penetrate the membrane and stain the cell. Cell death was recognized by deep staining of the nucleus. Failure to stain with trypan blue is also characteristic of the pale cell herein described. Hence the cell membrane of the pale cell is relatively intact, even though this may not be the primary cause for failure of

the cell to stain with gentian violet and safranine, which are both basic dyes [*10*]. The total conversion from pale- into dark-staining cells in incubated pus took only a few hours [*9*]. Our observations on cells incubated in a balanced salt solution relatively free of protein required considerably longer periods for similar conversion. It might be that proteolytic enzymes in the inflammatory exudate accelerate the reaction whereas urine more nearly resembles the salt solution. In the kidney, owing to the urine flow, migratory leukocytes may be excreted more rapidly and with less alteration than from other sites of deep inflammation in which secretions and edema fluid comprise the excretory medium. Similarly, pus obtained from clinically inflamed wounds differed from that in old uninflamed lesions by the higher proportion of pale cells. The pale-staining leukocyte in any secretion therefore might be considered a manifestation of acute or active inflammation. This explains its presence in the urine in pyelonephritis rather than in association with a lower urinary tract infection, an empiric observation to which there will be exceptions.

Some additional support for the thesis that associates pale-staining cells with inflammation can be drawn from the occurrence of each cell type in relation to the degree of pyuria and the specific gravity of the urine. (Fig. 2.) The number of cellular elements in a given volume of urine depends at least in part upon the relative rates of exudation and urine secretion. In the absence of an active inflammatory process the maximal number of cells per volume of urine should vary with the specific gravity, as was found true for dark-staining cells but not for pale cells. An active inflammatory lesion may generate a sufficient number of leukocytes to obscure the relationship, as was observed in the case of pale-staining cells.

If the pale cell is truly a sign of pyelonephritis or of an active inflammatory process, two practical conclusions can be drawn from the analysis: (1) With marked pyuria in urine of low specific gravity the leukocytes are invariably pale-staining cells. This finding in itself may be diagnostic of pyelonephritis. (2) Pale-staining cells may have great diagnostic significance in the early and subacute stages of chronic pyelonephritis in which less marked pyuria occurs in urine of high specific gravity, but in these instances the pale cells have non-motile cytoplasmic granules.

The correlation between the renal biopsy diagnosis and the staining behavior of the white cells in the urine sediment is important with regard to the question of whether or not pale-staining cells are of renal origin and indicate active inflammation. Perhaps the most important justification for scrutiny of this aspect of the investigation is that the degree of pyuria, *per se*, was found to be an unreliable guide to the presence of active chronic pyelonephritis, as were the patients' symptoms and qualitative bacterial cultures of the urine.

In our material pale cells were noted in the urine of all patients with pyelonephritis when repeated urinalyses were performed, but were noted in only 66 per cent when only a single random urinalysis was obtained; in other words, in two of three urinalyses per patient. Marked pale cell pyuria was encountered, most often in patients in whom renal biopsy showed significant infiltration of the interstitial tissue spaces with inflammatory cells.

Biopsy evidence of pyelonephritis was obtained in a few cases without pale cell pyuria in the urine specimens examined. In this group there were two patients with typical end-stage kidneys due to "chronic healed pyelonephritis" according to the classification of Weiss and Parker [*10*]. In four patients the urine specimens which were negative for pale cells were encountered after recent antibiotic therapy, and in other cases the disease was mild. It has been a common experience that treatment with an antibiotic reduces the degree of pale cell pyuria and that exacerbation or superinfection is accompanied by a sudden increase in the number of pale cells. Patients without pyelonephritis rarely excreted pale cells in the urine even though they exhibited pyuria and infected urine.

The absence of histologic evidence of pyelonephritis in a biopsy specimen does not exclude focal disease, and the finding of pale cell pyuria among a few such patients should be expected and is not incompatible with the meaning given to pale cells. Similar cells may enter the urine from the vagina, or with whole blood, and undoubtedly from the lower urinary tract upon occasion. Proper interpretation promises earlier and more accurate diagnosis of pyelonephritis.

SUMMARY

In a study of patients with infected urine who were shown by needle biopsy of the kidney to represent all stages of pyelonephritis, the gentian

violet and safranine stain described by Sternheimer and Malbin [2] was employed routinely to study the urine sediment. A correlation was found between renal parenchymal inflammation and the presence in the urine sediment of leukocytes with pale-staining characteristics.

Granular motility was found to be dependent upon the composition and osmolarity of the urine and occurred irregularly in pale-staining granulocytes. It was most striking in urines of low specific gravity. Various solutes added in increasing concentrations to the suspension medium differed in their capacity to inhibit granular motility.

The observations appear consistent with the hypothesis that pale cells in the urine usually come from the kidney and reflect the presence and, to some extent, the degree of acute inflammation present at the time of the examination. If this interpretation is correct vital granulocytes from the inflamed kidney rapidly appear in the urine, exhibiting only minor alteration of their staining characteristics. Granular motility is of incidental importance. Application of this concept was found to improve the validity of the clinical diagnosis of pyelonephritis as established by biopsy specimens from the kidney.

In the early stages of pyelonephritis, when the concentrating power of the kidney has not yet been jeopardized, the staining properties of the white blood cells in the urine sediment are of particular significance in diagnosis whereas the criterion of granular motility seems less important.

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Studies of Hyperuricemia Produced by Pyrazinamide*

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THE use of pyrazinamide in the treatment of pulmonary tuberculosis was first reported by Yeager et al. [*1*] in 1952. They noted the occurrence of pain and restricted joint motion without redness, swelling or tenderness in one-fourth of the patients they treated. Pyrazinamide was used in dosages varying from 2.8 to 8.4 gm. a day and the joint symptoms seemed to occur when the larger dosage regimens were used. Campagna and his co-workers [*2*], using the combination of pyrazinamide with isoniazid, also noted joint pains that were not accompanied by redness and swelling.

The occurrence of clinical gout in patients receiving chemotherapy for tuberculosis led us to investigate the possibility of an association between the gout and the antituberculous therapy the patients were receiving. As previously reported [*3*] we found that the serum uric acid was elevated in patients receiving pyrazinamide but not in patients being treated with other antituberculous drugs. This hyperuricemia was accompanied by a decreased urinary output of uric acid. Most patients tested were receiving isoniazid in addition to pyrazinamide. The serum uric acid was normal in those receiving isoniazid without pyrazinamide. The few patients examined, who were on a regimen of pyrazinamide without isoniazid, had serum uric acid levels at or just above the upper limit of normal. This led us to wonder if the isoniazid enhanced the hyperuricemic effects of pyrazinamide. However, it was also noted that four of five patients who received pyrazinamide without isoniazid were receiving PAS (*p*-aminosalicylic acid) in addition to other antituberculous drugs. (The fifth patient had an elevated uric acid on subsequent examination.) The less spectacular rise in the serum uric acid in these patients suggested the possibility that PAS retarded the elevation of the serum uric acid, possibly by acting as a uricosuric agent. It cast into doubt the notion that isoniazid enhanced the hyperuricemic effect of pyrazinamide.

It was in order to unravel the effects on the serum uric acid of these three antituberculous drugs, pyrazinamide, isoniazid and PAS, that the present study was undertaken. In addition it was thought that it might be profitable to determine whether probenecid could prevent or correct the hyperuricemia produced by pyrazinamide.

METHODS

The subjects selected for this study were ambulatory, hospitalized, male patients varying from twenty-three to sixty-eight years of age who did not have arthritis or findings suggestive of gout. Patients with evidence of renal or hepatic disease were excluded from the study. A negative cephalin flocculation test and a normal urine and non-protein nitrogen were minimal laboratory requirements for inclusion in the study. None of these patients were receiving any uricosuric agents except for an occasional aspirin tablet. The experiments were performed on six different groups of patients. Except for five tuberculous patients already on long-term therapy with pyrazinamide and isoniazid, and two patients who had been treated for tuberculosis in the past, these subjects were free of tuberculosis and were on the general medical wards. The five patients receiving long-term pyrazinamide-isoniazid therapy were used in the experiments to determine the effect of PAS and probenecid in persons already receiving pyrazinamide for many months. Three of these patients with tuberculosis were the only individuals used in more than one study. A new subject was added when the probenecid study was carried out to replace one no longer available for study.

The drugs were used in the following daily dosages: pyrazinamide, 3 gm.; isoniazid, 300 mg.; PAS, 12 gm. given in solution as the sodium salt, and probenecid, 2 gm. At first the drugs were changed at weekly intervals. Because it was feared that some uric acid changes might not have reached their peak within seven days, the first two studies were repeated chang-

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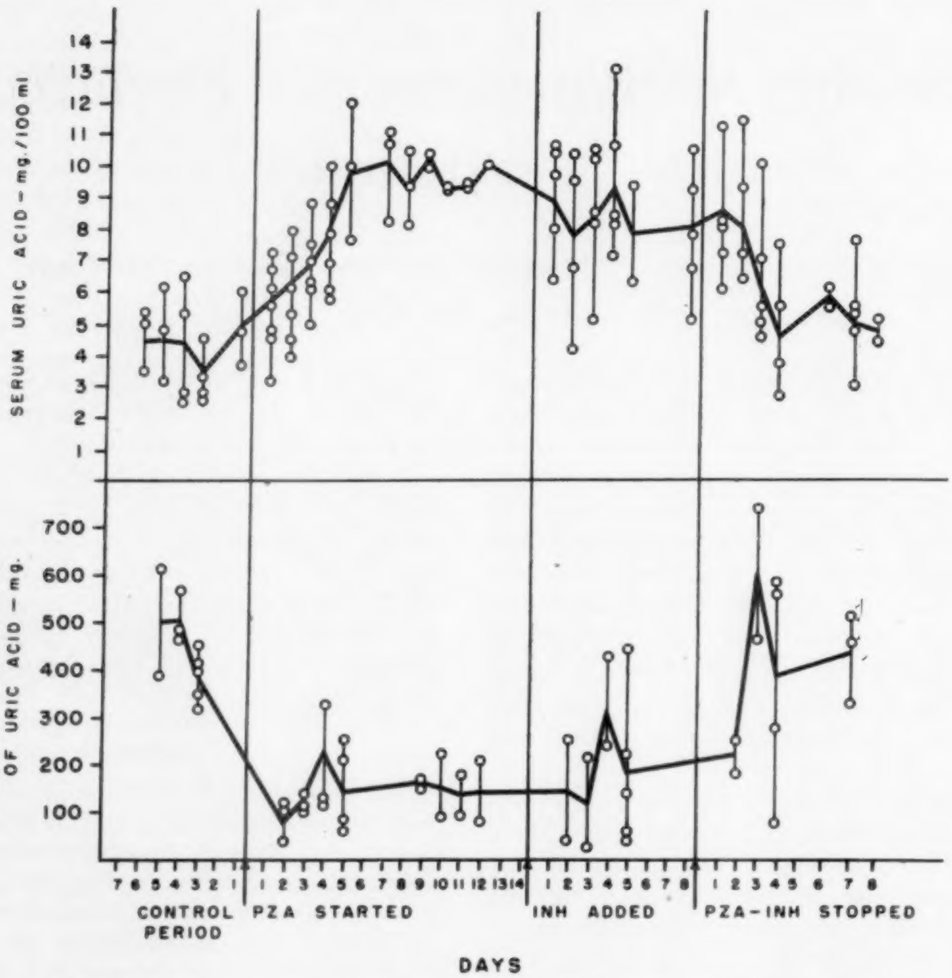

FIG. 1. Changes in the uric acid serum level and in the urinary output following administration of pyrazinamide (PZA) with later addition of isoniazid (INH).

ing the drugs at two-week intervals. Since it was found that the peak changes had occurred by the seventh day, the combined results are presented.

All patients were maintained on the regular hospital diet. A fasting blood specimen was obtained in the morning approximately sixteen hours after the last dose of medication. The serum was immediately separated and frozen. Urine specimens were collected in bottles containing sodium hydroxide pellets to maintain an alkaline state. Since the patients were ambulatory there was considerable concern about the reliability of the urine specimens. As a further check on the accuracy of the twenty-four-hour urine volumes, urinary creatinine determinations were made on a total of eighty-two specimens. In each subject the twenty-four-hour creatinine output was within 15 per cent of the mean in 68 per cent of the specimens.

The uric acid concentration of the serum and urine was determined by the method of Dubbs et al. [*4*] using the enzyme uricase and the Beckman DU spectrophotometer. As found in the previous study, the determination of serum uric acid concentration was unaffected by the *in vitro* addition of pyrazinamide or isoniazid. Inulin clearances were determined by the method of Alving and Miller [*5*].

RESULTS

Effect of Pyrazinamide and Subsequent Addition of Isoniazid. Figure 1 shows the effect of pyrazinamide on the serum uric acid level and twenty-four hour urinary output. It also shows the lack of effect of the addition of isoniazid on the hyperuricemia produced by pyrazinamide. The same basic scheme is used in all the figures to be presented. In the upper part of the figure is the serum uric acid concentration in mg. per 100 ml. and in the lower part is the twenty-four hour urinary output of uric acid in mg. The vertical bars represent the entire spread of values of all the subjects on any one day, and the open circles along the vertical bars are the individual values obtained in each patient on that day. The heavy graph line connects the mean value of each day's results. The vertical lines dividing the figure into

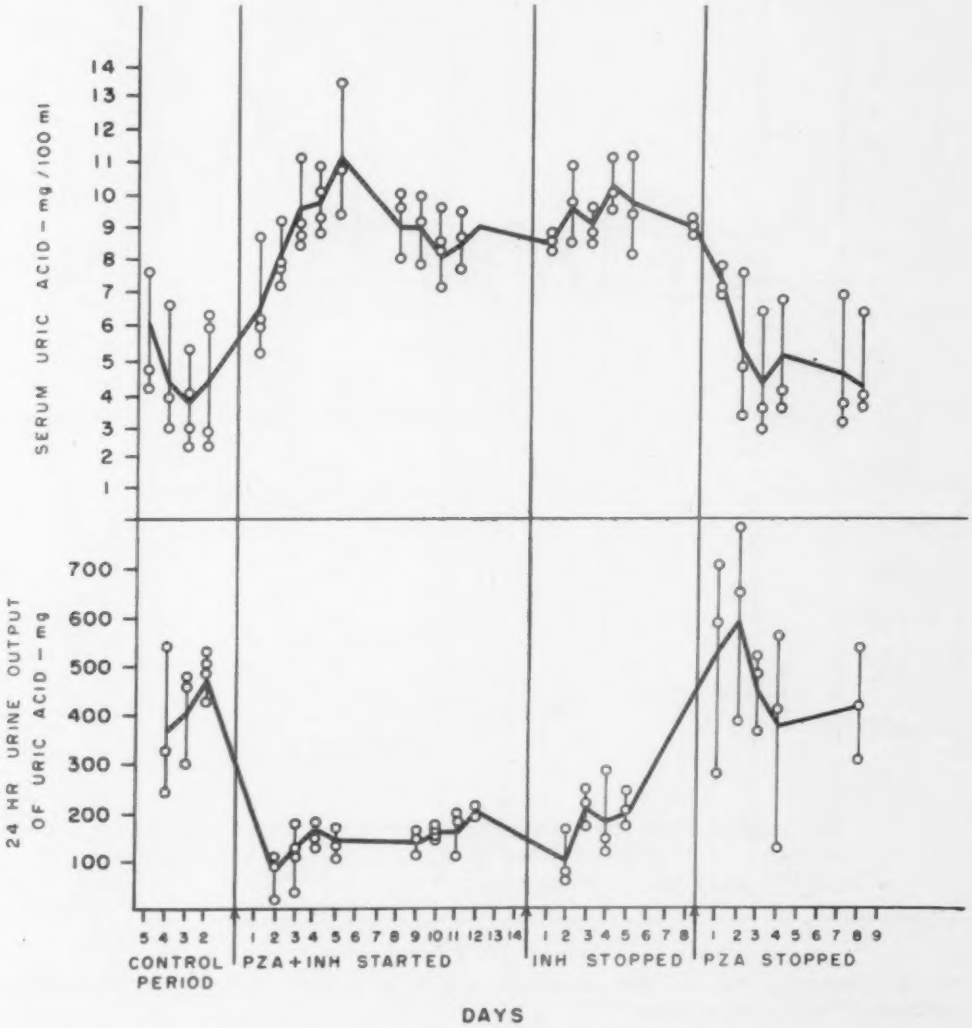

FIG. 2. Changes in the uric acid serum level and in the urinary output following administration of PZA plus INH then stopping INH.

sections indicate the time at which various drugs were started or stopped.

In Figure 1 it is seen that during the control period, presented to the left of the first vertical line, the mean serum uric acid level was about 4.5 mg. per 100 ml. and the twenty-four hour urinary output 400 to 500 mg. Pyrazinamide was started at the point indicated by the first vertical line. The urinary output of uric acid had fallen to 100 to 150 mg. by the second day. The serum uric acid rose more slowly, reaching a peak averaging slightly over 9 mg. per 100 ml. by the fifth to seventh day. Isoniazid was started at the point indicated by the second vertical line, the pyrazinamide being continued. There was no significant change in either the serum uric acid level or in the urinary output. After both pyrazinamide and isoniazid were discontinued at the point indicated by the third vertical line, the urinary output rose to 600 mg. of uric acid by the third day and the serum uric acid returned to the control level by the fourth day.

Inulin clearances were performed in two patients in this group, after they had been on both pyrazinamide and isoniazid for eight days, and were repeated nine days after both drugs had been discontinued (by which time the serum and urinary uric acid values had returned to normal). The glomerular filtration rate did not change significantly. In one subject the rates were 102 cc. and 100.5 cc., respectively, and in the other 149 cc. and 138 cc., respectively.

Effect of Pyrazinamide plus Isoniazid and Subsequent Stopping of Isoniazid. Figure 2 shows the effect of the combination of pyrazinamide and isoniazid on the uric acid level of the serum and urine. After pyrazinamide plus isoniazid was started, the serum uric acid reached a peak by

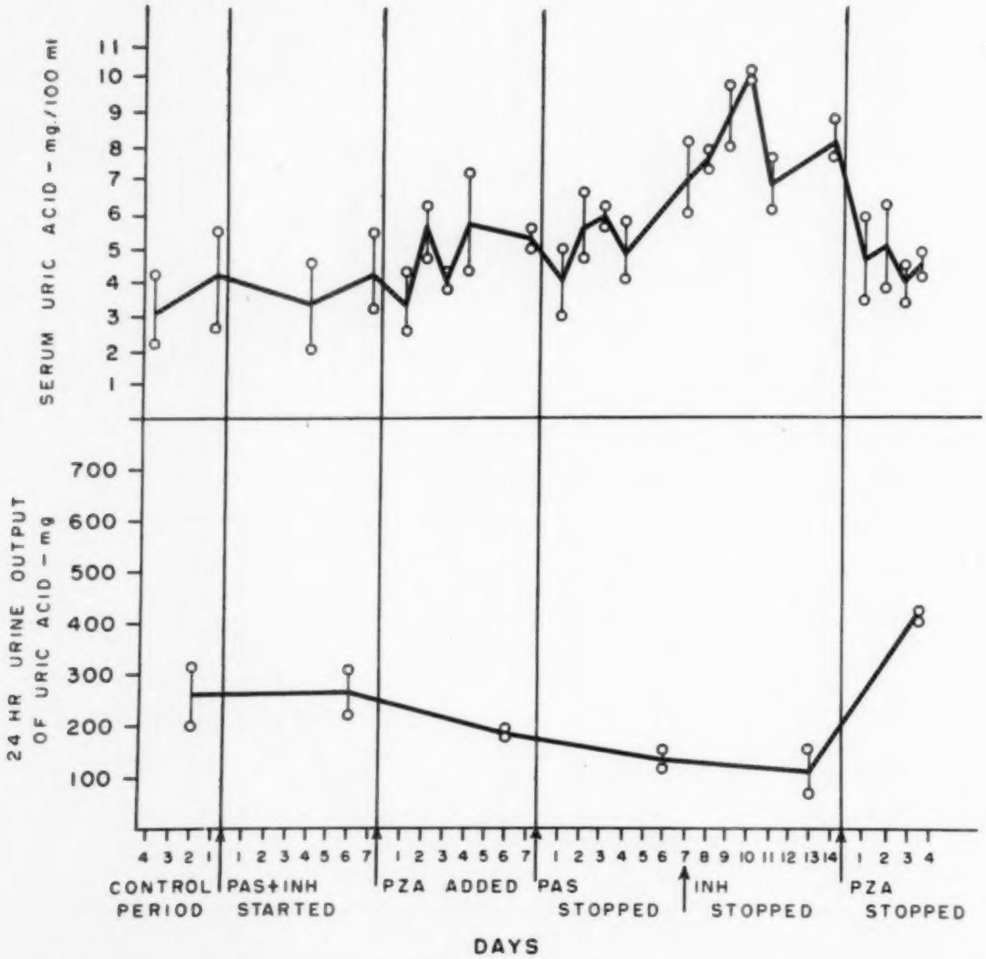

FIG. 3. Changes in the uric acid serum level and in the urinary output when para-aminosalicylate (PAS) is given before PZA.

the fifth day and then settled to an average of 9 mg. per 100 ml. of serum. The urinary output of uric acid fell immediately to 100 to 200 mg. in twenty-four hours. When the isoniazid was discontinued there was no significant change in either the serum uric acid or the urinary output. After the pyrazinamide was stopped the urinary output immediately rose, but the serum level took two to three days to return to the pretreatment value. There was no evidence in this or the previous experiment, presented in Figure 1, that isoniazid enhanced the hyperuricemic effects of pyrazinamide.

Effect of Addition of Pyrazinamide to PAS plus Isoniazid. Three patients were started on PAS and isoniazid after control values had been obtained. The serum and urinary uric acid remained unchanged. When pyrazinamide was given in addition to the other two drugs, one person responded, as in the previous two studies, with a rise in the serum uric acid to 9.5 mg. and a fall in urinary uric acid output. When the PAS was discontinued in this person there was no significant change in the blood or urinary findings during the next two weeks that pyrazinamide was continued.

The results in the other two patients in this group are shown in Figure 3. When pyrazinamide was added to these other two drugs the serum uric acid rose from an average of about 3.5 mg. per 100 ml. to 5 mg. per 100 ml. The urinary output of uric acid fell only slightly. Then PAS was discontinued. The serum uric acid did not rise until about seven days after PAS was stopped, and took three more days to reach its peak. The urinary output fell still further. When pyrazinamide was finally discontinued the uric acid values returned to the control level. In view of the previous studies it is not believed that the discontinuation of isoniazid seven days after the PAS was stopped had any significant effect on the serum or urinary uric acid. At the

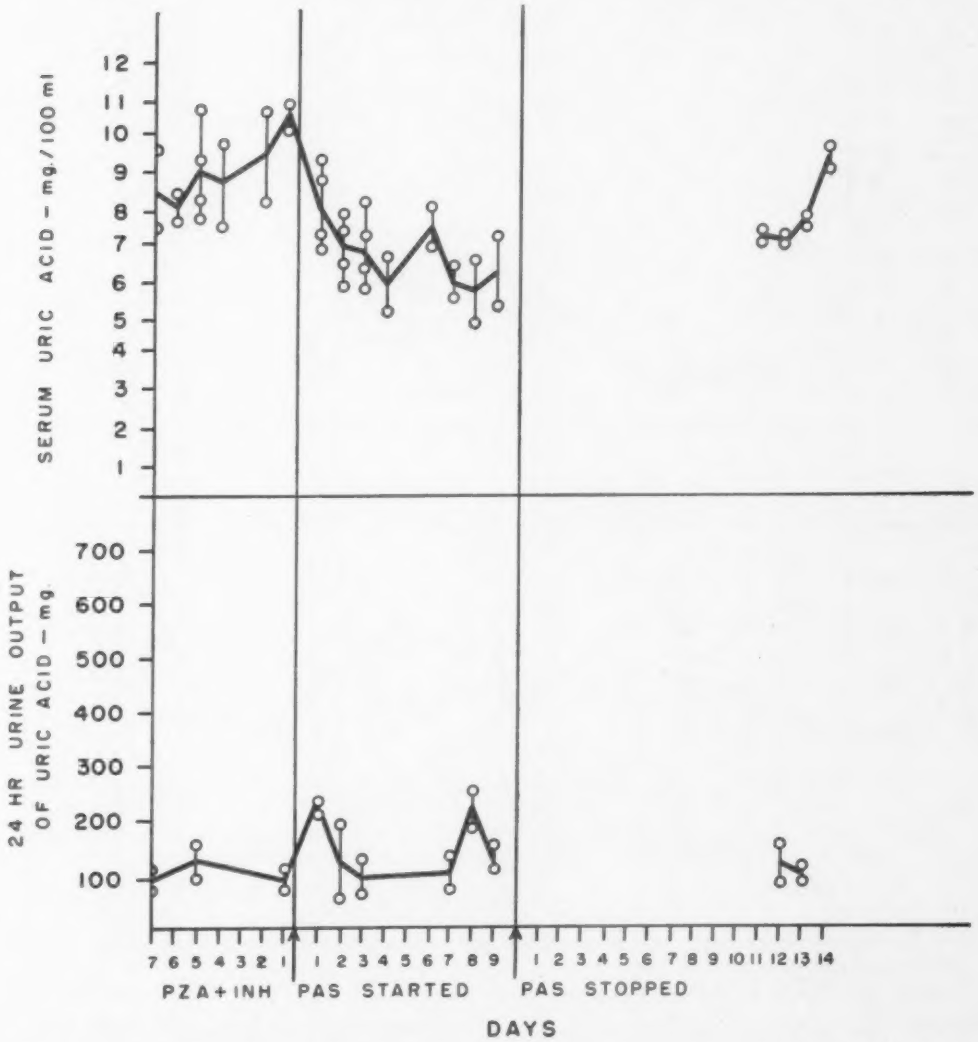

FIG. 4. Changes in the uric acid serum level and in the urinary output when PZA is given before PAS.

time we did this study we thought we could stop each drug a week apart without any overlap of their effects. However, when the results were obtained we found that the PAS effect persisted beyond seven days. In two of three subjects tested PAS suppressed the hyperuricemia produced by pyrazinamide. The effect of PAS on uric acid excretion was not great enough to be conclusive.

Effect of Addition of PAS to Pyrazinamide plus Isoniazid. Seven patients were tested. Four of these were patients with tuberculosis who had been receiving pyrazinamide-isoniazid therapy for many months. The other three were non-tuberculous subjects receiving pyrazinamide plus isoniazid for seven days before PAS was added. In three patients the serum and urinary uric acid values were unchanged by the addition of PAS (two tuberculous and one non-tuberculous subject).

The results in four patients who showed a reduction in the serum uric acid level are shown in Figure 4. The serum uric acid fell after the addition of PAS from an average of 9 mg. per 100 ml. to an average of 6 mg. per 100 ml. The urinary output of uric acid showed a sporadic increase that was not great enough to be definitely significant. Uric acid determinations were again obtained in the two tuberculous patients eleven days after PAS was discontinued. At this time the serum uric acid was only 7 mg. per 100 ml., but it rose to 10 mg. within the next few days. The urinary output was low.

Effect of Addition of Pyrazinamide to Probenecid. Four subjects were given probenecid for seven days before pyrazinamide was added. All four showed a slight reduction in serum uric acid. The urinary changes were less consistent, some showing an increase, the others remaining un-

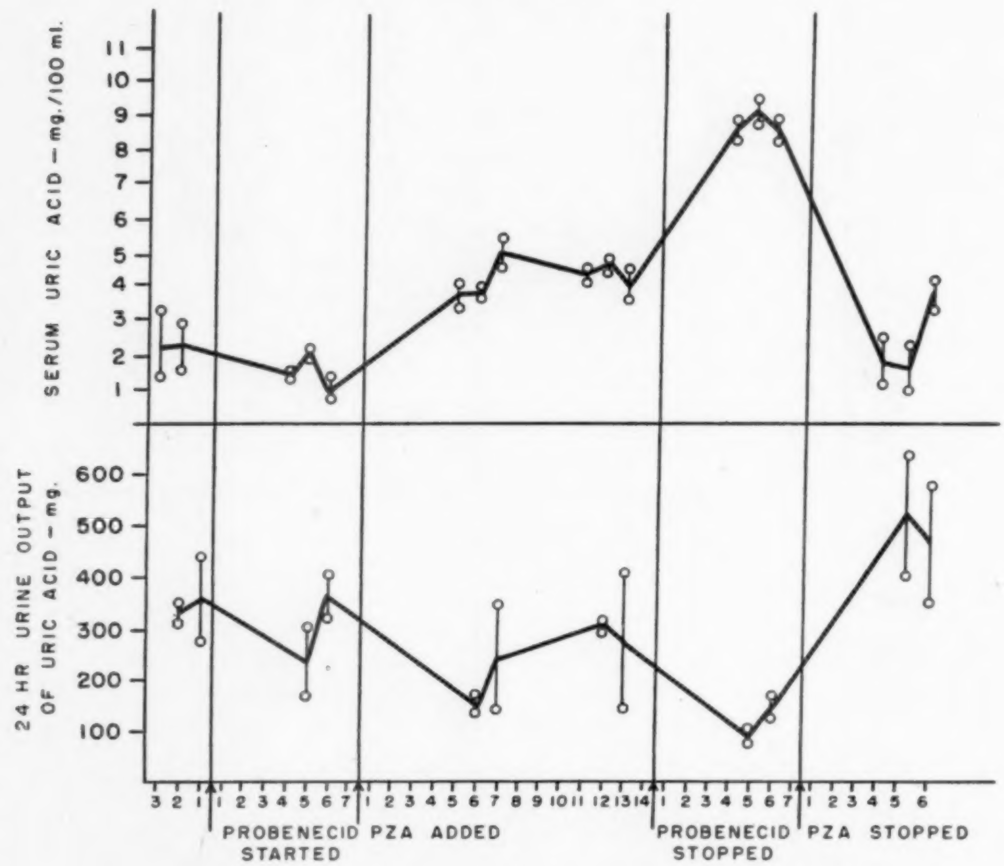

FIG. 5. Changes in the uric acid serum level and in the urinary output when probenecid is given before PZA.

changed. Since the urinary output was not measured until five days after probenecid was started, its uricosuric effect was probably missed in some subjects. As noted by Gutman and Yü [6] the uricosuria produced by probenecid only lasts a few days in normal subjects.

After pyrazinamide was added to the probenecid, two patients had a rise in the serum uric acid to over 9 mg. per 100 ml. with a fall in the twenty-four-hour urinary output of uric acid to below 200 mg. which continued unchanged during the three weeks pyrazinamide was given. Interestingly, the serum uric acid rise was late in occurring, not exceeding normal values until six and seven days, respectively, after the pyrazinamide was started.

The other two patients in this group had a suppression of the hyperuricemia produced by pyrazinamide as shown in Figure 5. After probenecid was started the serum uric acid fell slightly to 1.5 mg. per 100 ml. When pyrazinamide was given the uric acid rose to 5 mg. per 100 ml. and then remained constant. The urinary output showed a questionable decrease. When probenecid was stopped, fourteen days after the pyrazinamide was added, the serum uric acid rose to 9 mg. and the urinary output fell. When pyrazinamide was stopped the serum and urinary uric acid values returned to their pretreatment levels.

Effect of the Addition of Probenecid to Pyrazinamide plus Isoniazid. Four tuberculous patients who had been receiving pyrazinamide plus isoniazid for many months were given probenecid for twenty-eight days. Three of these had no significant change in the serum or urinary acid following the addition of probenecid to the other drugs nor was there any on its discontinuation.

One patient showed a fall in the serum uric acid from 7 mg. to an average of 5 mg. per 100 ml., as shown in Figure 6. The twenty-four hour urinary output increased from less than 100 mg. to almost 300 mg. of uric acid. When probenecid was discontinued the serum uric acid rose and the urinary output fell. It is interesting that three of these patients with

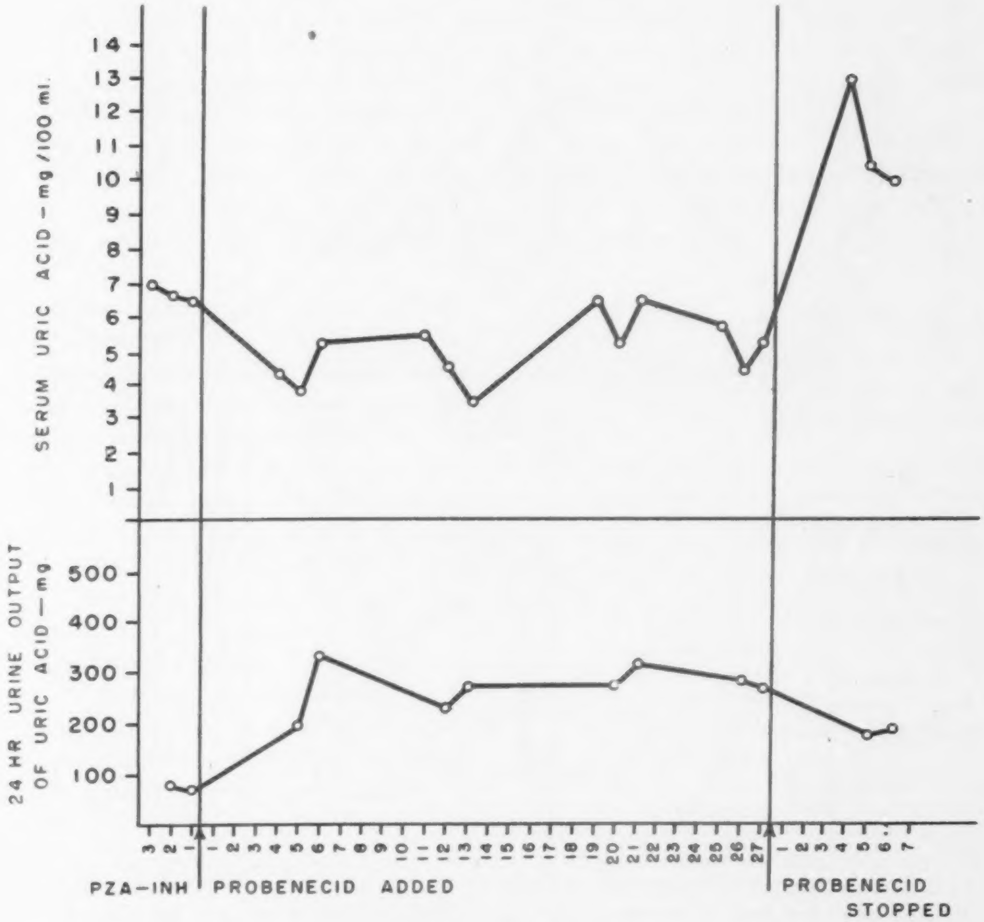

FIG. 6. Changes in the uric acid serum level and in the urinary output when PZA is given before probenecid.

tuberculosis were subjects in the previous experiment in which PAS was added to pyrazinamide and isoniazid. The patient who responded to probenecid was the only one of the three who responded to PAS administration, the other two responded to neither drug.

Effect of Addition to ACTH to Pyrazinamide. One subject was started, unbeknown to us, on ACTH, 80 units daily after receiving pyrazinamide for eight days. As shown in Figure 7, at the time ACTH was added the serum uric acid had risen to 8 mg. per 100 ml. and the uric acid urinary output was about 200 mg. daily. Following the administration of ACTH the urinary output of uric acid rose to 600 mg. by the second day and reached a peak of 900 mg. The serum uric acid fell slowly and steadily. The addition of isoniazid was without significant effect. Following the discontinuation of pyrazinamide and isoniazid there was no significant change in the serum or urinary uric acid values.

COMMENTS

The increase in the serum uric acid following the administration of pyrazinamide appears to be due to decreased excretion of uric acid in the urine. This decrease in the urinary output of uric acid was great enough to explain the rise in the serum level without the necessity of postulating an increased synthesis of uric acid as in primary gout [*7*] or its release by an increased destruction of cells such as may occur in erythrocytosis or leukemia. The serum uric acid level was unaffected by the pyrazinamide blood level, as shown by the unchanged values before and two hours after the morning dose of pyrazinamide [*3*]. In addition, Allison [*8*] has found an increase in serum uric acid to an average of 9 mg. per 100 ml. of serum when giving 1.5 gm. of pyrazinamide daily, which is one-half of the amount we used.

Normally there is almost complete filtration of

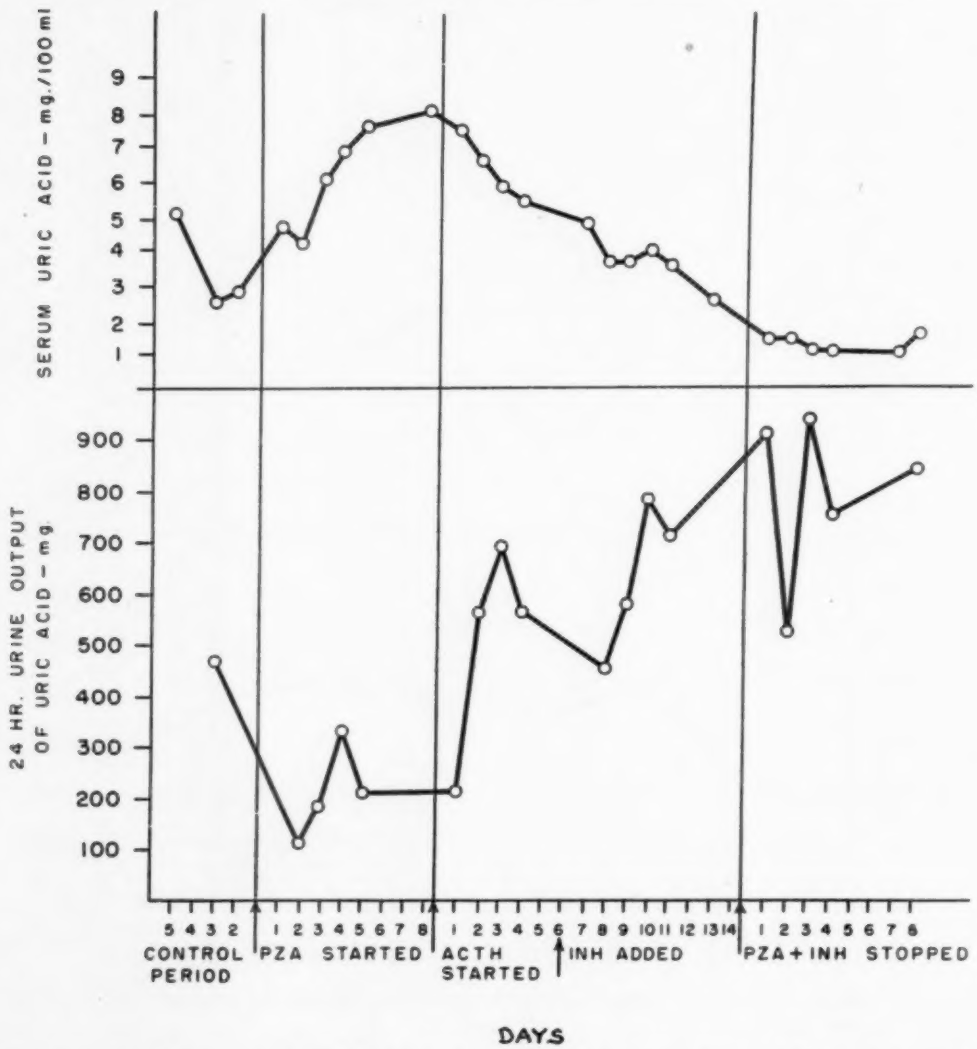

Fig. 7. Uric acid changes in the patient who received PZA with later addition of ACTH.

urate at the glomerulus with subsequent tubular reabsorption by enzymatic transfer systems of all but 5 to 10 per cent of the filtered urate [6]. Apparently when pyrazinamide is administered there is even greater tubular reabsorption of urates. The unchanged inulin clearances suggest that glomerular function is unaffected. Gleason et al. [9] found a decrease in phenolsulfonphthalein excretion during pyrazinamide administration, which is consistent with a tubular effect.

Since the serum uric acid remains elevated and the urinary output remains low as long as the pyrazinamide is continued, one would suspect that uric acid is deposited in the tissues, increasing the miscible pool. Measurements of the miscible pool of uric acid, similar to those made by Benedict et al. [10], before and during long-term pyrazinamide therapy, would be interesting. There are often considerable day to day changes in the serum and urinary uric acid levels with periods of up to a week when the serum uric acid might be as low as 6 mg. per 100 ml. The urinary output rarely rises above 300 mg. in twenty-four hours.

It becomes apparent that pyrazinamide, PAS and probenecid all affect the enzymatic tubular transport mechanism related to uric acid reabsorption. It is not surprising that PAS may be uricosuric as it is structurally related to benzoic, salicylic and p-aminobenzoic acids [11]. In addition, probenecid, another benzoic acid derivative, causes retention of PAS [12]. It is unlikely that any uricosuric properties of PAS are due to liberation of free salicylates, as very little, if any, are formed in the metabolism of PAS [13]. On reflection the failure of probenecid always to prevent the hyperuricemia produced by pyrazinamide might have been anticipated. It is well known that when salicylates are given with probenecid the expected uricosuria fails to appear [14,15]. In view of the demonstration by

Yü and Gutman [*16*] that uricosuric agents in small enough doses cause uric acid retention, it might be anticipated that pyrazinamide may be uricosuric if given in large enough doses. It is known that ACTH is a potent uricosuric agent [*6,10*]. Its effect in the patient tested demonstrates that the uric acid retention by the kidney can be reversed even though pyrazinamide is continued.

The relationship between the attacks of gout and the hyperuricemia is probably an indirect one, as is true in primary gout [*6*]. In spite of the continuation of pyrazinamide therapy and the persistence of the hyperuricemia there was no recurrence of gout in the two patients we studied [*3*]. Perhaps in some or in all of these patients an inapparent gouty diathesis is present. We gave pyrazinamide for seven days to one patient without tuberculosis soon after he had recovered from an acute attack of gout that had responded to colchicine. Although his serum uric acid rose to 19 mg. per 100 ml. there was no recurrence of acute gouty arthritis either during administration of pyrazinamide or after it was discontinued.

In spite of the occurrence of an occasional attack of gout during pyrazinamide therapy for tuberculosis, one cannot at this time condemn this drug as harmful to most patients on the basis of the hyperuricemia alone. Renal damage has not occurred in our patients and seems to be unlikely unless the renal tubule is damaged as a result of altered uric acid transport. In view of the low urinary output of uric acid, renal stones would not be expected. Although we have not observed the occurrence of uric acid tophi, they might be expected if the pyrazinamide, and therefore the hyperuricemia, was maintained long enough.

SUMMARY

1. The serum uric acid becomes elevated following administration of pyrazinamide. This is associated with a decrease in the urinary output of uric acid to one-third to one-half the control level.

2. Inulin clearances were unchanged by pyrazinamide in the two patients tested, suggesting that the renal effect was tubular, not glomerular.

3. Isoniazid had no effect on the hyperuricemic properties of pyrazinamide.

4. Para-aminosalicylate, in some but by no means in all the subjects, reduced the hyperuricemic effects of pyrazinamide. There was suggestive but far from conclusive evidence that PAS was uricosuric.

5. Probenecid reduced the hyperuricemic effect of pyrazinamide in only some of the subjects tested. It was no more effective in this regard than PAS.

6. In the one patient tested, ACTH was markedly uricosuric and completely reversed the serum and urinary uric acid changes produced by pyrazinamide.

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Hyperuricemia Due to Pyrazinamide*

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HYPERURICEMIA may occur as a result of an increase in production of uric acid or of inadequate excretion of this end-product of purine metabolism. It is known that lactic acid, ergotamine, atropine and posterior pituitary solution decrease the excretion of uric acid, but very few drugs are directly responsible for hyperuricemia [*1*]. The antifolic acid compounds, e.g., aminopterin, and the newer purine analogues (6-mercaptopurine, thioguanine, 6-chloropurine and 2,6-diamino-purine) cause hyperuricemia by releasing excessive amounts of nucleo-protein from cellular destruction [*2*]. The antituberculous agent, pyrazinamide, may now be added to the list of drugs causing hyperuricemia.

Following the demonstration of the activity of nicotinamide against Mycobacterium tuberculosis, Kushner et al. [*3*] studied a similar group of compounds known as the pyrazine derivatives. By ammonolysing methyl pyrazinate they produced pyrazinamide. After animal experimentation had proved its efficacy, Yeager et al. [*4*] reported its use in forty-three patients with pulmonary tuberculosis. Thirteen patients in this group complained of joint pains. Other reports mentioned joint pains without clinical evidence of articular involvement [*5–7*]. In reporting three cases of clinical gout occurring while the patients were on pyrazinamide therapy, Cullen et al. [*8*] noted hyperuricemia in all patients receiving this drug. Similar findings were noted in another case but the gout and elevated uric acid levels were thought to be related to isoniazid which the patient had been receiving [*9*]. In another patient, routine investigation after passage of a non-urate calculus revealed hyperuricemia after two months of pyrazinamide therapy [*10*].

METHODS

Groups of patients with pulmonary tuberculosis being treated with bedrest and chemotherapy were studied. Various combinations of the antituberculous agents streptomycin, isoniazid, para-aminosalicylic acid and pyrazinamide were used in the following dosages: streptomycin, 1 gm., intramuscularly twice weekly; isoniazid, 100 mg., three times a day; para-aminosalicylic acid, 4 gm., three times a day; and pyrazinamide, 0.5 gm. or 1.0 gm., three times a day, orally. All patients had normal hepatic and renal function as determined by cephalin flocculation test, thymol turbidity test, bromsulphalein® excretion, blood urea nitrogen determinations and urinalyses. Complete hemograms were performed in each patient and all values were essentially within normal limits. All patients were maintained on the regular hospital diet consisting of 107 gm. of protein, 290 gm. of carbohydrate and 175 gm. of fat to yield approximately 3,200 calories.

Serum uric acid determinations were performed by a modified Koch's method [*11*]. Other reducing substances such as glutathione and ergothionine found mostly in red blood cells interfere with the specificity of this test. By using blood serum rather than whole blood, this error is minimized. Normal values in this laboratory are from 3.0 to 5.5 mg. per 100 ml. of blood. To rule out any reducing action of the drug itself on the phosphotungstate reagent, both pyrazinamide and its breakdown product, pyrazinoic acid, were tested, with negative results.

STUDY

Patients Receiving Pyrazinamide (PZA). Hyperuricemia was found in forty-six patients receiving pyrazinamide alone, or with isoniazid, or with isoniazid and streptomycin. In a group of ten patients the serum uric acid was determined at varying intervals of PZA therapy and repeat levels were obtained two weeks later. Persistent hyperuricemia was noted in all cases, with values ranging from 6.2 to 9.7 mg. per cent. This elevation was produced with either 1.5 or 3.0 gm. of PZA daily. (Table I.)

Ten random patients not receiving PZA were used as controls, and serum uric acid levels obtained at the same time were less than 5.5 mg. per cent in every instance.

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Patients with no Previous Chemotherapy. This group consisted of eleven new patients admitted for treatment. All serum uric acid levels were below 5.4 mg. per cent. However, following institution of PZA therapy in daily dosage of either 1.5 gm. or 3.0 gm. and isoniazid 100 mg., three times a day, hyperuricemia promptly occurred. (Table II.)

TABLE I
URIC ACID LEVELS IN PATIENTS RECEIVING PYRAZINAMIDE (PZA)

Case No.	Age of Patient (yr.)	Daily Dosage of PZA (gm.)	Duration of PZA Therapy (weeks)	Serum Uric Acid Level (mg. %)	Uric Acid Level 2 Weeks Later (mg. %)
1	58	1.5	16	7.6	7.1
2	23	3.0	6	7.8	8.5
3	33	3.0	13	9.3	8.0
4	59	1.5	8	6.2	7.6
5	28	3.0	3	9.7	9.7
6	44	3.0	12	7.2	6.6
7	27	3.0	3	9.4	7.2
8	67	1.5	1½	7.7	8.8
9	24	1.5	4	8.5	6.4
10	36	3.0	5	7.5	7.3

TABLE II
DEVELOPMENT OF HYPERURICEMIA FOLLOWING INSTITUTION OF PZA THERAPY

Case No.	Daily Dose of PZA (gm.)	Pre-treatment Serum Uric Acid Levels (mg. %)	Serum Uric Acid Levels (mg. %)	Days PZA Therapy
11	3.0	4.0	8.7	1
12	1.5	3.0	7.7	8
13	1.5	3.6	8.9	6
14	1.5	2.5	7.8	7
15	3.0	3.9	7.1	1
16	3.0	5.4	6.3	1
17	3.0	4.6	9.1	10
18	3.0	3.0	11.6	11
19	3.0	5.0	6.9	9
20	3.0	5.5	9.0	8
21	3.0	4.8	7.3	5

Patients Receiving Other Antituberculous Drugs. Eight patients receiving streptomycin and isoniazid had normal serum uric acid levels. They were then given 3 gm. of PZA daily and within forty-eight hours all patients were found to have hyperuricemia. (Table III.)

Five patients receiving isoniazid and PAS had normal serum uric acid levels. When PZA in doses of 3 gm. daily was added to their chemotherapeutic regimen, slight changes were noted in twenty-four and in forty-eight hours but after nine days all serum uric acid levels were definitely elevated. (Table III.) It is concluded that PAS delayed but did not prevent the appearance of hyperuricemia.

TABLE III
SERUM URIC ACID LEVELS AFTER ADDITION OF PYRAZINAMIDE (PZA) TO OTHER ANTITUBERCULOUS DRUGS

Case No.	Pre-treatment Serum Uric Acid Levels (mg. %)	Serum Uric Acid after 24 Hours of PZA (mg. %)	Serum Uric Acid after 48 Hours PZA (mg. %)	Serum Uric Acid after 9 Days PZA (mg. %)
Streptomycin and Isoniazid Group				
22	3.7	6.6	7.9	...
23	4.1	5.3	6.8	...
24	4.7	6.9	8.1	...
25	4.8	7.4	8.3	...
26	4.9	5.9	7.4	...
27	4.1	7.3	7.8	...
28	3.5	6.3	6.9	...
29	5.4	9.1	8.8	...
Isoniazid and Para-aminosalicylate Group				
30	5.0	5.8	5.9	8.5
31	4.2	5.2	5.1	5.9
32	3.6	5.1	4.7	7.0
33	5.1	6.1	6.2	8.0
34	5.3	5.4	5.7	8.4

Effect of Aspirin and Salicylates. In one patient treated with streptomycin and isoniazid, hyperuricemia failed to develop after PZA therapy. This patient had been receiving prolonged sodium salicylate therapy for arthritis. Two patients without tuberculosis received acetylsalicylic acid in dosage of 0.6 gm. four times a day. They did not receive tuberculostatic drugs. Control serum uric acid values were normal. The addition of 3.0 gm. of pyrazinamide daily did not produce an elevation of serum uric acid, presumably because of the uricosuric effect of aspirin. (Fig. 1.)

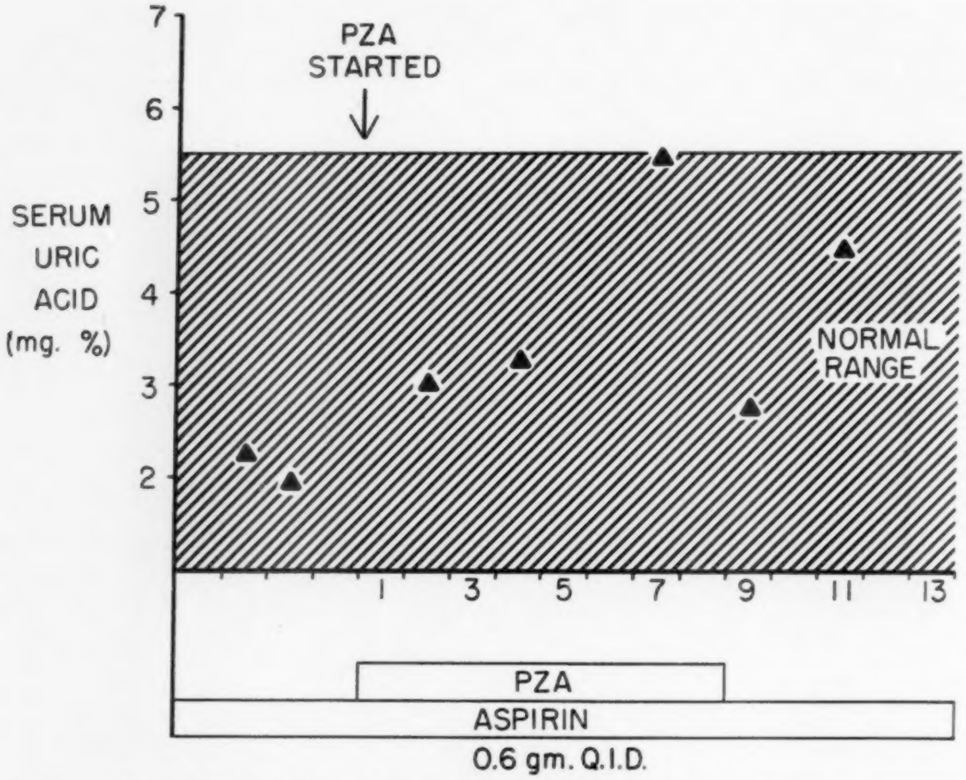

FIG. 1. Effect of aspirin in preventing PZA-induced hyperuricemia.

TABLE IV
EFFECT OF PROBENECID (BENEMID) ON PZA-INDUCED HYPERURICEMIA

Case No.	Pre-Benemid Serum Uric Acid Levels (mg. %)	Serum Uric Acid after 3 Days of Benemid (mg. %)	Serum Uric Acid after 7 Days of Benemid (mg. %)	Serum Uric Acid after 14 Days of Benemid (mg. %)
1	7.7	6.1	7.0	8.5
2	7.5	4.3	4.3	5.6
5	10.0	7.1	5.8	7.9
7	7.1	4.7	4.5	6.0
9	5.8	3.7	4.4	5.2
11	7.9	7.4	6.9	6.5
14	7.3	5.2	5.0	7.2
16	9.3	7.5	8.6	7.1
17	10.5	5.9	6.7	8.3
23	6.7	7.3	6.2	7.5
24	7.7	7.7	6.7	8.2
25	11.0	9.6	9.3	11.1
35	9.3	7.5	7.3	9.5
36	7.9	6.7	5.8	6.4

Effect of Probenecid (Benemid®). Fourteen patients with PZA-induced hyperuricemia in this study were given benemid, 0.5 gm. three times a day, after uric acid levels had been repeated. Following three days of therapy, only four patients showed a return to normal levels. By the fifteenth day, hyperuricemic levels were again present in thirteen cases. (Table IV.)

At no time throughout the course of this study did any patients complain of joint pains or exhibit any manifestations of gout.

SUMMARY AND CONCLUSIONS

1. The use of the antituberculous agent, pyrazinamide, in daily doses of 1.5 gm. or 3.0 gm. resulted in a persistent hyperuricemia.

2. Coincidental administration of other tuberculostatic drugs, such as streptomycin, isoniazid or para-aminosalicylate, did not prevent this PZA-induced hyperuricemia, although para-aminosalicylate did delay elevation of serum uric acid.

3. Probenecid (benemid) caused an initial lowering of elevated levels in a few cases but continued use did not prevent the return of PZA-induced hyperuricemia.

4. In patients receiving sodium salicylate or aspirin, pyrazinamide failed to produce an elevation of serum uric acid levels.

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Renal Function in Gout*

With a Commentary on the Renal Regulation of Urate Excretion, and the Role of the Kidney in the Pathogenesis of Gout

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KNOWLEDGE of the functional state of the kidneys in the progressive stages of gout still suffers from an insufficiency of data and from some confusion of opinion. The subject is of some significance. Quite apart from its intrinsic interest as a reflection of the structural changes of the "gouty kidney," it relates to one of the central problems in the pathogenesis of gout. This is the question whether hyperuricemia, the hallmark of the disorder, is attributable to an inherent renal defect specifically of urate excretion, or to a metabolic error characterized by overproduction of urate; in the latter instance such impairment of renal function as may be present could then be ascribed, in part, to the effects of the metabolic defect.

The concept that the primary cause of gout is a specific impairment of the capacity of the kidney to excrete uric acid, and that the rate of urate production is of secondary importance, was first proposed in 1848 by Garrod upon the occasion of his historic announcement of the discovery of hyperuricemia as a characteristic of the disorder [*1*]. As his exposition of this view has not since been surpassed, it is cited here:

"The results of these experiments on the condition of the blood and urine . . . appear to indicate that . . . urea and uric acid are separately eliminated; also that one of these functions may be impaired or destroyed, the other remaining entire. . . . In gout, the uric-acid-excreting function being defective, chalk-like deposits are produced by a vicarious discharge of urate of soda. Gout would thus appear, at least partly, to depend on a loss of power (temporary or permanent) in the uric-acid-excreting function of the kidneys; the premonitory symptoms, and those also which constitute the paroxysm, arising from an excess of this acid in the blood, and the effort to expel the *materies morbi* from the system. Any undue formation of this compound would favour the occurrence of the disease, and hence the connection between gout, gravel, and calculus, hence also the influence of high living, wine, porter, want of exercise, and other like causes, in inducing it. This hypothesis also explains two facts, which have been regarded as militating against the humoral pathology of the affection, namely, its hereditary nature, and its frequent occurrence in low states of the system; for we can understand that the peculiarity of the kidney with reference to the excretion of uric acid may be transmitted, and likewise, that when the function in question is permanently injured, it will not require an excessive formation of this acid to cause its accumulation in the blood."

The principal support for this view has come from reports indicating that the hyperuricemia of gouty subjects is associated with urinary urate excretion within the limits of normal variation, and often less than normal, as would be expected if deficient renal excretion of urate were the cause. Thus Brugsch and Schittenhelm [*2*] in 1907 reviewed the available data (obtained by often imperfect precipitation technics) in thirty-five gouty subjects, and concluded that the urinary urate excretion was less than normal (0.01 to 0.3 gm./twenty-four hours) in 43 per cent, within the usual normal limits (0.3 to 0.4 gm./twenty-four hours) in 36 per cent, and within the upper limits of normal (0.4 to 0.6 gm./twenty-four hours) in 21 per cent. In a later compilation Pratt [*3*] found a mean "endogenous" urate excretion in twenty gouty subjects of 250 mg./twenty-four hours as compared with a mean normal figure of 390 mg./twenty-four hours. So far as can be ascertained, these older determinations apparently dealt for the most part with more advanced cases of gout in which

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the ravages of disease and age might well have led to renal impairment and hence to interference with excretion of urate by the kidneys.

Subsequent reports, of results with more reliable analytic methods in a wider spectrum of patients, confirmed the fact that most gouty subjects excrete normal, sometimes even subnormal quantities of urate in the urine, but disclosed generally higher mean levels of urate excretion, and an occasional gouty patient with markedly excessive urate output. Thus Folin, Berglund and Derick [*4*] in 1924 reported augmented excretion, of 687, 889 and 958 mg./twenty-four hours, significantly higher than their normal range of 425 to 605 mg./twenty-four hours, in three of nine patients with gout. Brøchner-Mortensen [*5*], using his ferricyanide method, found the mean endogenous urinary urate excretion in eleven gouty subjects to be 414 mg./twenty-four hours (range, 297 to 680 mg.), somewhat higher than the mean of 374 mg./twenty-four hours (range, 269 to 532 mg.) in twenty normal persons. In 1938 Talbott and Coombs [*6*] reported a urinary urate excretion of "more than 2 Gm." daily in two young gouty patients while taking a low purine diet, in contrast to "less than 1 Gm." daily in two non-gouty subjects on a similar diet. In 1950 Friedman and Byers [7] found a mean urinary excretion in five young gouty subjects of 567 mg./twenty-four hours (range, 472 to 613 mg.) as compared with a mean of 398 mg./twenty-four hours (range 360 to 438 mg.) in six normal individuals. Talbott and Coombs [*6*] and Friedman and Byers [7] both stressed the point that their gouty subjects with greater than normal urinary urate excretion were relatively young and free of any indication of renal insufficiency. They inferred that the renal impairment so frequently encountered in older gouty subjects might well depress the elimination of urate by the kidneys, the major organ of urate excretion, and thus mask excessive urate production.

Preliminary reports of our own measurements of the twenty-four-hour urinary urate excretion in gouty subjects [*8,9*] amplify and, for the most part, support these findings. The basal urinary urate excretion in the majority of the fifty-five cases of gout reported in 1952 [*9*] was within the normal range but the mean, 531 ± 177 mg./twenty-four hours, was higher than that of thirteen non-gouty control subjects, 416 ± 68 mg./twenty-four hours. Twenty-four of these patients had overt renal damage; the range of their twenty-four-hour urinary urate excretion was 190 to 751 mg., with a mean of 436 ± 142 mg. Thirty-one patients, rather widely distributed as to age, duration of manifest gout and presence or absence of visible tophaceous deposits, had no proteinuria, urinary casts, phenolsulfonphthalein retention or azotemia; the range of twenty-four-hour urinary urate excretion in these cases was 389 to 999 mg., with a significantly elevated mean of 605 ± 172 mg. In eighteen of the gouty subjects the urinary urate excretion, while taking a low purine, meat-free diet, was in excess of 620 mg./twenty-four hours, a quantity 3 standard deviations above the normal mean. Repeated determinations under closely supervised conditions diminished the possibility of error in these cases due to surreptitious purine or drug intake, sporadic passage of urate gravel, or gross mistakes in urine collection or chemical analysis. It would therefore appear that a significant minority of patients with gout regularly excrete excessive quantities of urate in the urine while on a basal diet, that this is neither an altogether sporadic and anomalous occurrence nor a constant manifestation of the disorder in younger subjects. The inference that at least in such gouty subjects excessive quantities of urate are synthesized from precursors [*8*] was established in two instances by the direct demonstration of excessive incorporation of glycine-N^{15} into urate [*10,11*]. These isotope experiments failed, however, to give any indication of overproduction of urate in gouty subjects not excreting excessive amounts of urate in the urine; and these, as already indicated, make up the majority of cases.

The urate clearance measurements reported in the literature reveal no distinct difference between gouty and non-gouty subjects. Thus Brøchner-Mortensen [*5,12*] found the urate clearance in seventeen of twenty cases of gout to be either within the limits of normal variation or, when there was marked reduction in the urea and creatinine clearances, depressed to not less than 60 per cent of normal. Coombs et al. [*13*] and Talbott [*14*] noted no distinct impairment of the ability of the kidneys to clear urate in twenty-seven gouty patients as compared with fifty-five non-gouty control subjects. Friedman and Byers [*7*] found a normal urate clearance in six of eight cases of gout. These investigators pointed out the inconsistency in associating normal urate clearance with normal urinary urate excretion: "an unchanged or normal urate

clearance in an individual with elevated plasma content of urate (as in the gouty patient) indicates an increase in the actual amount of urate excreted" [7].

Coombs et al. [13] further emphasized that the percentage of filtered urate reabsorbed by the tubules was the same, approximately 90 per cent, in gouty and in non-gouty subjects with "normal kidney function"; severe impairment in kidney function was associated in both gouty and non-gouty subjects with a decline in the percentage of filtered urate reabsorbed. Coombs et al. [13] concluded from their clearance studies that although "based upon certain assumptions, the proof for which is not available . . . the data show no differential inability of the kidneys to clear urate in gouty patients. . . . No constitutional inferiority of the kidneys to excrete urate was demonstrated. . . . Kidney changes in patients with gout are believed to be the result and not the cause of the metabolic dyscrasia."

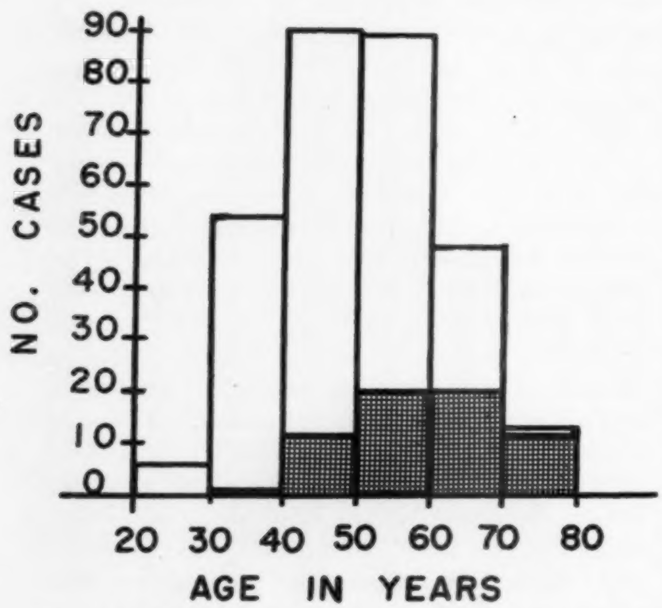

FIG. 1. Distribution of 300 gouty subjects according to age. The presence of overt renal damage, as defined in the text, is indicated by cross-hatching. The proportion of patients with overt renal damage increased with age.

The present enquiry comes to similar conclusions. But perhaps the experimental data herein assembled, in patients representative of the several phases of the disorder, will serve further to elucidate the mechanisms of renal excretion of urate, and the recurrent question of a primary defect in the capacity of the kidneys of the gouty subject to eliminate urate.

METHODS

The diagnosis of primary gout in the 300 patients selected for study was made on the basis of clinical criteria (history or presence of characteristic acute arthritis responsive to colchicine) and the demonstration of hyperuricemia, defined as not less than 6.5 mg. per cent in men and 5.0 mg. per cent in women by the analytic method employed. In addition, 142 patients had tophi, visible in most cases but in sixteen instances demonstrable only in roentgenograms. The age range at the time of study was twenty-five to seventy-nine years; the age distribution is indicated in Figure 1. Nine women are included in this series.

Routine urine analysis, a concentration test, a phenolsulfonphthalein excretion test and a serum non-protein nitrogen determination were performed in every instance. Judged by these criteria, sixty-five patients, most of them in the older age groups, gave evidence of overt renal disease. Of these two were known to have chronic glomerular nephritis, three had polycystic kidneys, seventeen had hypertensive cardiovascular disease, sixteen had had coronary thrombosis, four had had cerebral thrombosis, nine had nephrolithiasis with more or less associated pyelonephritis. Of the 235 gouty subjects free of overt renal disease by these criteria, twenty-seven had or had had nephrolithiasis, sixteen had hypertension, thirteen had had coronary thrombosis, two had had cerebral thrombosis.

Inulin and urate clearances were measured in 150 of these gouty subjects, all men; in 110 cases the clearance of para-aminohippurate was concurrently determined, and in fourteen cases Tm_{PAH} was measured. Twenty-one subjects were studied more than once. Urate and inulin clearances were obtained also in twelve non-gouty subjects. Urine collections were made by catheterization of the bladder, and standard renal clearance technics [15] were employed throughout. Prior to study the patients had been taking low purine, restricted protein diets for varying periods of time.

In addition, one-hour urate and creatinine clearance measurements were made in sixty-four other gouty (male) patients and in forty-nine normal male and fifty-two normal female control subjects. All such clearance studies were carried out with the subject in the postabsorptive state. Liberal water intake was provided to ensure adequate urine flow. Spontaneously voided urine was collected for sixty minutes. Blood samples were obtained at the beginning and at end of the clearance period, and the blood and urine samples were analyzed for urate and creatinine.

Twenty-four hour urine collections were made in 300 gouty subjects after they had taken a low purine, meat-free diet for one to two or more weeks. The diet was calculated to contain approximately 60 gm. protein (derived chiefly from milk, milk products and cereals), 60 gm. fat, and sufficient carbohydrate to provide a total of 1,600 to 2,000 calories per day. The

TABLE I

RESULTS OF RENAL CLEARANCE STUDIES IN 150 GOUTY SUBJECTS

(Arranged in descending order of filtered urate load, F_{urate}. Values not corrected to standard body surface area.)

No.	Age	Body Surface Area (sq. meter)	Tophi	P_{urate} (mg. %)	C_{inulin} (ml./min.)	C_{PAH} (ml./min.)	F_{urate} (mg./min.)	UV_{urate} (μg./min.)	T_{urate} (mg./min.)	C_{urate} (ml./min.)	Urinary Urate (mg./24 hr.)	Remarks
1.	44	2.20	+	11.1	159	629	17.6	1011	16.6	9.3	743	...
2.	39	2.30	++	10.6	164	624	17.4	1148	16.3	10.9	1520	Nephrolithiasis
3.	37	2.18	+	10.7	138	603	16.1	739	15.4	6.9	583	...
4.	43	2.26	±	10.8	146	...	15.8	615	15.2	5.5	499	...
5.	30	2.07	0	11.9	128	...	15.2	1657	13.5	14.4	1034	Coronary thrombosis
6.	35	2.08	0	9.8	154	...	15.1	807	14.3	8.2	550	...
7.	42	2.16	0	8.4	158	...	15.1	583	14.5	7.1	526	...
8.	33	2.12	+	11.2	132	532	14.8	950	13.8	8.4	647	Nephrolithiasis
9.	41	2.52	++	9.7	151	493	14.6	565	14.0	5.8	649	Hypertensive cardiovascular disease
10.	34	1.98	±	13.4	109	423	14.6	1320	13.3	11.0	681	Nephrolithiasis
11.	47	2.13	0	9.7	150	485	14.6	685	13.9	7.1	420	...
12.	44	2.17	0	8.9	163	665	14.5	805	13.7	12.1	512	Tm_{PAH} 79.0 mg./minute
13.	40	2.22	0	9.8	147	578	14.4	702	13.7	7.6	832	...
14.	47	2.06	0	9.4	149	603	14.0	960	13.0	9.3	584	...
15.	33	2.13	0	11.7	120	439	14.0	705	13.3	6.2	918	...
16.	39	2.21	0	10.8	126	660	13.6	982	12.6	9.1	972	...
17.	39	2.10	0	9.1	149	588	13.6	807	12.8	9.2	466	...
18.	41	2.03	+	9.4	145	...	13.6	886	12.7	9.8	914	...
19.	39	2.30	0	9.8	138	681	13.5	935	12.6	9.5	940	...
20.	37	2.06	0	8.7	154	531	13.4	482	12.9	7.3	409	Hypertensive cardiovascular disease
21.	47	1.90	+	12.4	108	473	13.4	1009	12.4	8.0	1412	Nephrolithiasis
22.	33	2.10	0	10.2	130	772	13.3	1050	12.2	10.3	1069	...
23.	30	1.90	0	9.2	145	668	13.3	728	12.6	7.9	374	...
24.	36	2.25	0	7.6	174	658	13.2	784	12.4	10.2	....	...
25.	42	2.04	±	10.0	132	661	13.2	1182	12.0	11.8	774	Tm_{PAH} 87.5 mg./minute
26.	38	1.84	±	11.0	119	517	13.1	1385	11.7	12.6	888	...
27.	42	1.84	±	10.0	130	544	13.0	684	12.3	6.8	602	...
28.	41	2.24	+	8.2	159	...	13.0	520	12.5	6.2	520	...
29.	33	1.83	0	9.4	138	624	13.0	1044	12.0	11.2	579	...
30.	42	1.88	0	9.3	138	573	12.8	671	12.1	7.2	495	...
31.	44	2.21	+	10.8	117	...	12.6	900	11.7	8.3	695	...
32.	50	1.96	+	8.4	150	507	12.6	607	12.0	7.3	536	...
33.	39	2.19	0	9.0	140	676	12.6	700	11.9	7.8	513	...
34.	69	1.73	0	10.9	115	722	12.5	868	11.6	8.1	457	...
35.	37	2.01	++	10.8	115	...	12.4	444	12.0	4.2	545	Tm_{PAH} 80.5 mg./minute
36.	41	2.05	0	9.5	128	622	12.2	516	11.7	7.2	632	...
37.	44	2.03	0	9.5	127	...	12.1	1115	11.0	12.0	590	...
38.	52	2.21	0	8.2	147	...	12.1	891	11.2	12.5	705	...
39.	32	2.24	0	8.5	141	628	12.0	695	11.3	8.2	626	...
40.	41	1.96	0	8.7	136	545	11.8	757	11.0	7.9	450	...
41.	42	1.81	0	9.4	124	...	11.7	447	11.2	4.9	335	...
42.	54	1.90	0	8.6	136	515	11.7	545	11.2	6.3	339	...
43.	47	2.10	0	7.7	150	577	11.6	733	10.9	9.5	425	Tm_{PAH} 88.8 mg./minute
44.	34	1.86	++	10.1	115	620	11.6	499	11.1	5.0	610	Nephrolithiasis

Table I (*Continued*)

RESULTS OF RENAL CLEARANCE STUDIES IN 150 GOUTY SUBJECTS

No.	Age	Body Surface Area (sq. meter)	Tophi	P_{urate} (mg. %)	C_{inulin} (ml./min.)	C_{PAH} (ml./min.)	F_{urate} (mg./min.)	UV_{urate} (μg./min.)	T_{urate} (mg./min.)	C_{urate} (ml./min.)	Urinary Urate (mg./24 hr.)	Remarks
45.	35	2.03	0	9.1	126	624	11.5	1280	10.2	14.1	676	....
46.	40	2.07	0	10.6	108	378	11.4	612	10.8	5.8	758	....
47.	38	1.88	++	10.0	113	622	11.3	575	10.7	5.8	455	Tm_{PAH} 73.6 mg./minute
48.	73	1.98	0	7.3	153	...	11.2	500	10.7	6.8	515	....
49.	44	1.95	0	8.2	135	...	11.1	411	10.7	5.1	646	....
50.	52	1.79	0	8.7	128	530	11.1	578	10.6	8.9	383	Nephrolithiasis
51.	43	2.13	0	8.0	137	...	11.0	1044	10.0	13.2	632	....
52.	34	1.94	0	8.7	126	536	11.0	638	10.3	7.4	362	Tm_{PAH} 75.2 mg./minute
53.	47	2.01	0	9.9	111	468	11.0	1027	10.0	10.3	446	Tm_{PAH} 77.7 mg./minute
54.	45	1.69	+	9.9	110	416	10.9	485	10.4	4.8	....	....
55.	33	1.95	0	10.5	104	491	10.9	811	10.1	7.7	604	....
56.	25	1.98	0	8.3	131	673	10.9	559	10.3	8.3	470	Tm_{PAH} 74.3 mg./minute
57.	58	1.83	0	8.5	127	...	10.8	722	10.1	8.9	348	....
58.	45	1.87	0	9.6	111	...	10.7	510	10.2	5.3	....	....
59.	56	1.74	++	8.4	127	417	10.7	560	10.1	6.7	622	....
60.	52	1.72	+	11.3	94.5	350	10.7	952	9.7	8.5	628	Hypertensive cardiovascular disease Tm_{PAH} 40.3 mg./minute
61.	33	1.93	0	8.6	124	590	10.7	656	10.0	7.6	479	....
62.	44	1.97	+	11.5	92.9	...	10.7	1021	9.7	8.9	765	Nephrolithiasis
63.	52	1.91	0	12.1	88.8	385	10.6	530	10.1	4.4	305	....
64.	45	2.03	++	10.7	97.7	469	10.5	485	10.0	4.5	446	....
65.	52	1.72	0	9.8	106	402	10.4	1027	9.4	10.5	537	....
66.	47	1.78	+++	13.7	75.1	...	10.3	846	9.5	6.3	519	....
67.	40	1.84	++	8.4	122	530	10.2	563	9.6	6.7	638	....
68.	54	2.09	0	9.1	112	...	10.2	627	9.6	6.8	763	....
69.	49	2.13	+	8.7	117	546	10.2	540	9.7	6.2	345	....
70.	34	2.16	+	9.2	151	...	10.1	790	9.3	8.6	335	....
71.	48	2.04	0	10.0	101	406	10.1	795	9.3	8.0	442	....
72.	28	2.14	0	7.8	129	...	10.1	363	9.7	4.6	471	....
73.	52	1.83	0	8.9	114	...	10.1	553	9.6	6.2	548	Coronary thrombosis
74.	43	1.93	0	8.9	112	...	10.0	586	9.4	6.6	443	....
75.	60	1.88	0	9.3	106	...	9.9	614	9.3	7.1	585	....
76.	61	2.09	0	7.8	126	444	9.8	792	9.0	10.2	....	Hypertensive cardiovascular disease
77.	40	2.03	0	9.2	107	512	9.8	752	9.0	8.2	792	....
78.	41	2.03	0	7.4	132	...	9.8	504	9.3	9.7	495	....
79.	55	1.79	+++	10.9	89.0	306	9.7	604	9.1	5.5	644	....
80.	39	2.04	0	9.1	106	392	9.6	672	8.9	7.4	575	Nephrolithiasis
81.	46	2.24	+	7.3	132	...	9.6	604	9.0	8.3	523	....
82.	44	2.08	+++	11.5	83.7	289	9.6	767	8.8	6.7	335	Chronic nephritis
83.	47	1.80	0	7.4	128	...	9.5	708	8.8	9.7	368	Nephrolithiasis, hypertensive cardiovascular disease
84.	39	1.94	0	8.0	117	...	9.5	403	9.1	5.8	432	....
85.	52	1.85	0	8.4	113	472	9.5	450	9.0	5.4	495	....

TABLE I (*Continued*)

RESULTS OF RENAL CLEARANCE STUDIES IN 150 GOUTY SUBJECTS

No.	Age	Body Surface Area (sq. meter)	Tophi	P_{urate} (mg. %)	C_{inulin} (ml./min.)	C_{PAH} (ml./min.)	F_{urate} (mg./min.)	UV_{urate} (μg./min.)	T_{urate} (mg./min.)	C_{urate} (ml./min.)	Urinary Urate (mg./24 hr.)	Remarks
86.	53	2.18	+	8.4	112	435	9.4	617	8.8	7.3	413	Hypertensive cardiovascular disease, nephrolithiasis
87.	32	2.08	0	8.4	112	...	9.4	763	8.6	9.0	848	....
88.	54	1.88	0	9.8	96.3	453	9.4	666	8.7	9.4	577	Nephrolithiasis
89.	38	1.66	+	10.7	87.4	443	9.4	596	8.8	5.7	....	....
90.	56	2.05	0	7.4	126	462	9.3	885	8.4	11.9	560	Hypertensive cardiovascular disease
91.	45	1.91	0	8.4	111	456	9.3	549	8.8	6.5	508	....
92.	37	1.82	0	7.1	130	479	9.2	756	8.4	10.6	368	....
93.	28	1.69	+	10.1	90.5	484	9.1	480	8.7	9.6	343	....
94.	60	1.66	0	8.4	108	495	9.1	751	8.3	8.9	....	....
95.	43	1.96	0	7.0	130	...	9.1	586	8.5	8.5	645	Coronary thrombosis
96.	52	1.95	0	7.5	112	486	9.0	491	8.5	6.5	542	....
97.	51	1.78	0	7.1	125	458	8.9	705	8.2	9.9	350	....
98.	35	2.20	0	9.1	97.6	465	8.9	703	8.2	7.7	552	....
99.	65	1.86	0	7.5	118	...	8.9	465	8.4	6.2	....	....
100.	54	1.98	++	10.0	88.2	423	8.8	1120	7.7	11.2	681	....
101.	47	1.90	0	8.6	102	449	8.8	290	8.5	3.1	462	....
102.	38	1.90	0	8.7	101	533	8.8	532	8.3	6.2	536	....
103.	57	1.86	0	9.9	88.1	388	8.7	447	8.3	4.5	589	....
104.	30	2.04	+	11.0	78.0	386	8.6	514	8.1	4.7	340	....
105.	65	1.99	+	9.2	92.6	295	8.5	659	7.8	7.1	445	Nephrolithiasis, nephrosclerosis
106.	61	1.88	0	8.0	105	...	8.4	440	8.0	5.5	389	....
107.	53	1.94	0	9.3	90.6	448	8.4	409	8.0	4.8	488	....
108.	49	1.74	0	7.9	106	...	8.4	415	8.0	5.2	396	Chronic nephritis
109.	44	2.04	0	9.8	83.7	288	8.2	426	7.8	4.4	380	Hypertensive cardiovascular disease
110.	60	1.89	0	9.2	89.2	371	8.2	503	7.7	5.8	332	....
111.	36	1.96	+	8.0	96.9	427	8.2	431	7.8	4.3	551	....
112.	62	1.97	+++	8.7	92.8	326	8.1	245	7.8	2.8	400	....
113.	37	1.95	0	6.9	118	...	8.1	554	7.5	8.0	535	....
114.	48	2.01	0	7.6	106	444	8.1	611	7.5	8.1	363	Hypertensive cardiovascular disease
115.	49	1.82	±	8.7	93.6	...	8.1	633	7.5	7.5	578	Nephrolithiasis
116.	54	1.80	0	9.5	83.7	...	8.0	735	7.3	7.8	633	Hypertensive cardiovascular disease
117.	55	2.06	++	9.7	82.6	349	8.0	544	7.5	5.3	527	Hypertensive cardiovascular disease
118.	57	1.95	0	10.0	77.9	374	7.8	530	7.3	5.3	258	....
119.	49	1.93	0	7.6	105	535	7.8	626	7.2	8.3	314	....
120.	63	1.81	0	9.2	85.1	316	7.8	257	7.5	2.8	422	Coronary thrombosis
121.	46	1.86	0	8.7	88.5	414	7.7	764	6.9	9.0	662	....
122.	31	2.02	0	5.4	143	655	7.7	678	7.0	12.6	....	....
123.	49	1.79	0	8.8	85.8	318	7.6	581	7.0	6.6	372	Hypertensive cardiovascular disease
124.	35	1.85	0	8.5	87.2	414	7.4	766	6.6	9.0	581	....
125.	47	1.91	0	6.7	111	465	7.4	866	6.6	12.8	442	....
126.	38	1.78	+	6.8	107	...	7.3	544	6.8	8.0	480	Nephrolithiasis
127.	37	1.92	0	6.8	107	549	7.3	688	6.6	10.3	404	....

TABLE I (*Continued*)

RESULTS OF RENAL CLEARANCE STUDIES IN 150 GOUTY SUBJECTS

No.	Age	Body Surface Area (sq. meter)	Tophi	P_{urate} (mg. %)	C_{inulin} (ml./min.)	C_{PAH} (ml./min.)	F_{urate} (mg./min.)	UV_{urate} (µg./min.)	T_{urate} (mg./min.)	C_{urate} (ml./min.)	Urinary Urate (mg./24 hr.)	Remarks
128.	57	1.96	0	8.8	82.7	350	7.3	424	6.9	4.8	338	Nephrosclerosis, Tm_{PAH} 61.4 mg./minute
129.	45	1.68	0	8.3	86.9	452	7.2	620	6.6	7.5	460	....
130.	50	1.76	0	7.5	93.5	498	7.0	415	6.6	5.8	457	....
131.	65	1.81	0	7.7	90.0	...	6.9	402	6.5	5.2	....	Nephrolithiasis
132.	53	1.91	0	9.4	72.8	255	6.8	855	5.9	9.2	503	Hypertensive cardiovascular disease, nephrolithiasis Tm_{PAH} 39.7 mg./minute
133.	59	1.79	++	8.1	83.2	417	6.7	652	6.0	8.4	555	Coronary thrombosis
134.	49	1.94	0	5.9	111	512	6.5	438	6.1	7.4	486	....
135.	37	1.73	0	9.2	70.6	299	6.5	633	5.9	6.7	408	....
136.	60	1.61	+++	8.9	71.8	326	6.4	322	6.1	3.8	204	Nephrosclerosis
137.	61	1.78	0	7.3	86.2	411	6.3	402	5.9	5.5	323	....
138.	42	1.78	+	8.2	76.8	423	6.3	337	6.0	4.2	388	Tm_{PAH} 65.0 mg./minute
139.	60	1.98	++	11.2	54.4	242	6.1	512	5.6	4.8	442	Coronary thrombosis
140.	64	1.90	0	8.4	72.7	322	6.1	463	5.7	8.1	466	Nephrosclerosis, nephrolithiasis
141.	68	1.84	0	7.9	76.3	302	6.0	468	5.6	5.9	409	Nephrosclerosis, Tm_{PAH} 75.2 mg./minute
142.	58	1.94	++	7.6	77.3	299	5.9	460	5.4	6.1	407	Coronary thrombosis, Tm_{PAH} 67.5 mg./minute
143.	58	1.76	0	8.6	66.6	328	5.7	558	5.2	4.8	375	....
144.	65	1.66	++	7.6	71.4	289	5.4	286	5.1	3.8	194	Nephrosclerosis
145.	47	1.86	0	5.3	100	...	5.3	549	4.8	10.4	652	....
146.	58	1.65	+	8.7	58.8	202	5.1	414	4.7	4.8	269	Nephrosclerosis
147.	59	1.89	+	9.9	52.0	230	5.1	495	4.7	5.2	476	Nephrosclerosis, cerebral thrombosis
148.	53	1.67	+++	6.1	81.4	...	5.0	407	4.6	6.6	588	Nephrosclerosis
149.	65	1.90	0	6.5	76.4	322	5.0	339	4.6	5.2	....	Nephrosclerosis
150.	63	1.71	+++	8.8	50.4	...	4.4	429	4.0	5.0	360	Nephrosclerosis

NOTE: F_{urate} = filtered urate load, T_{urate} = calculated urate reabsorbed by the tubules, assuming no tubular excretion of urate.

urate excretion figures cited represent means of determinations in at least two 24-hour collections.

Hyperuricemic relatives of some of our gouty subjects also were studied to represent the gouty trait in the stage of asymptomatic "essential" hyperuricemia, before the onset of acute gouty arthritis. Data on the twenty-four hour urinary urate excretion while on a low purine, meat-free diet were obtained in five instances; one-hour renal clearances of urate and creatinine in six; and standard simultaneous clearances of inulin and urate in seven, in four of whom C_{PAH} also was determined.

The determinations of urate in urine and blood were made by a modification of the colorimetric method of Buchanan, Block and Christman incorporating the use of uricase, with correction for non-urate chromogens in urine. The details of the method are given elsewhere [*16*], as is the evidence for satisfactory agreement with spectrophotometric measurement at mµ 292. Data on the incorporation of glycine-N^{15} into urinary urate in H. G. were obtained by the procedure previously described [*10*].

RESULTS

Glomerular Filtration Rate, Effective Renal Plasma Flow, Tubular Excretory Capacity (Tm_{PAH}). The inulin clearance was measured in 150 gouty subjects (Table I), mean age forty-six years. C_{inulin}, corrected to standard body surface area,

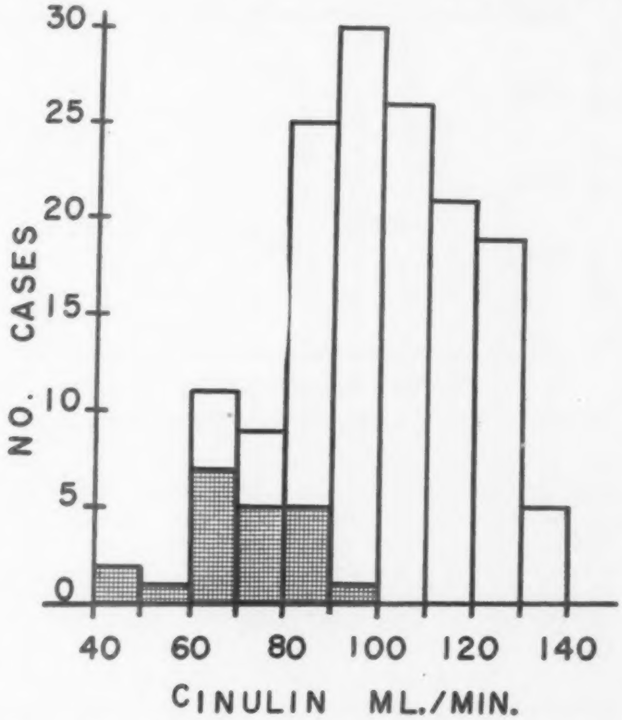

FIG. 2. Distribution of C_{inulin} data in 150 gouty subjects. The presence of overt renal damage, as defined in the text, is indicated by cross-hatching.

varied widely, from 134 to 47.3 ml./minute, mean 98.5 ± 17.7 ml./minute. The distribution of values, indicated in Figure 2, shows a preponderance within the low normal range, and less than 90 ml./minute in forty-eight instances; a distribution in general agreement with that previously recorded by Coombs et al. [13].

Comparison with the distribution of C_{inulin} data in non-gouty subjects of equivalent age [17] reveals a close general correspondence, particularly in the older age groups with distinctly reduced mean C_{inulin}. (Fig. 3.)* This suggests that such decline in glomerular filtration rate as may occur in gouty subjects usually is not ascribable to the effects of gout *per se* but to degenerative changes in the renal vasculature associated with aging and related causes. In support of this interpretation is the finding that of twenty-three

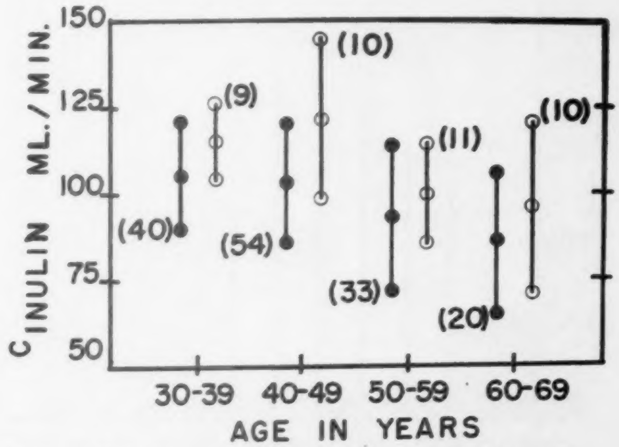

FIG. 3. Relation of C_{inulin} to age in 147 gouty subjects (solid dots) compared with normal subjects of corresponding age (hollow dots), taken from Davies and Shock [17]. The means and standard deviations of distribution are shown (dots) for each gouty and non-gouty group. The numbers in parentheses indicate the number of subjects in each group.

patients with an inulin clearance less than 80 ml./minute, fifteen were of advanced age or had essential hypertension or manifest coronary heart disease.

C_{PAH} was measured in 110 of these gouty subjects. (Table I.) Figure 4 indicates the distribution of the values (after correction to standard body surface area, range 722 to 208 ml./minute, mean 414 ± 90.0 ml./minute). A comparison with the distribution in non-gouty subjects of equivalent age [17], made in Figure 5, indicates a moderate but significant reduction in effective renal plasma flow ($p < 0.01$ in all age groups) in patients with gout.* That this reduction may be disproportionate to the glomerular filtration rate, at least in the more advanced age groups, is indicated by the calculated mean filtration fractions: ages twenty to twenty-nine years, 0.19; thirty to thirty-nine years, 0.23; forty to forty-nine years, 0.24; fifty to fifty-nine years, 0.25; sixty to sixty-nine years, 0.25. The significance of the apparent decline in renal plasma flow and the rise in filtration fraction in many of these cases is speculative. Arterial hypertension was present in about half of the patients with

* In this comparison, some allowance probably should be made for the modest fall in glomerular filtration rate, and particularly in renal plasma flow, which is apt to occur on a meat-free diet [18], taken by the gouty subjects but not by the nongouty subjects in question, and for the possibility of overcorrection when the body surface area of some of our grossly overweight gouty subjects was converted to standard (mean calculated body surface area in this series, 1.95 M^2). In connection with the C_{PAH} data, a tendency to higher packed red cell volume in gouty subjects also should be taken into account in translating the results into renal blood flow.

* See footnote in opposite column.

statistically significant increase in the filtration fraction.

Tm_{PAH} was measured in fourteen gouty subjects. (Table I.) The data, corrected to standard body surface area, indicate a mean of 62.3 ± 10.4 mg./minute (range, 74.7 to 39.7 mg./minute), with a preponderance of values within the low normal range, and less than 60 mg./minute in three instances. The four patients in whom the lowest Tm_{PAH} values were obtained all had presumptive renal vascular disease. The ratios C_{inulin}/Tm_{PAH} remained for the most part within the limits of normal variation [*18*], the mean value being 1.58 ± 0.35. The mean ratio C_{PAH}/Tm_{PAH} was 6.63 ± 1.49, suggesting reduction ($p < 0.01$), attributable chiefly to low values in four patients with presumptive renal vascular disease.

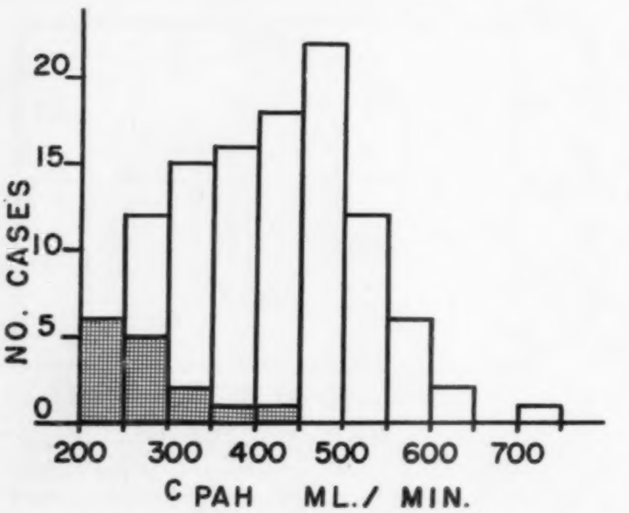

FIG. 4. Distribution of C_{PAH} data in 110 gouty subjects. The presence of overt renal damage, as defined in the text, is indicated by cross-hatching.

Excretion of Urate. The filtered urate load: Since the plasma urate may be assumed to be virtually wholly filtrable at the glomerulus [*19*], the quantity, milligrams urate filtered per minute, may be calculated as the product of the glomerular filtration rate (inulin clearance, ml./minute) and the plasma urate concentration (mg./ml.).

The mean urate level in 105 apparently normal adult males, average age thirty-seven years, was found to be 5.6 ± 1.3 mg. per cent (that of 103 normal adult females, average age thirty-seven years, was 4.3 ± 0.9 mg. per cent). The mean inulin clearance of men in the forty to forty-nine year age group, according to Davies and Shock [*17*], is 121.2 ± 23.3 ml./minute. The mean filtered urate load may therefore be estimated to approximate 6.8 mg./minute in normal adult males of the age span comparable to that of our gouty patients. Values of this magnitude were obtained by direct determination in non-gouty subjects. In forty-nine adult males, one-hour urate and creatinine clearance measurements gave an estimated mean filtered urate load of 6.7 ± 1.4 mg./minute. In twelve adult males, urate and inulin clearance measurements by standard technics gave an estimated mean filtered urate load of 6.3 ± 1.4 mg./minute.

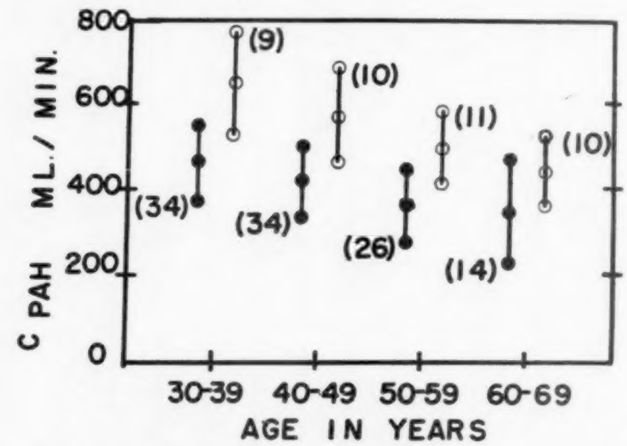

FIG. 5. Relation of C_{PAH} to age in 108 gouty subjects (solid dots) compared with normal subjects of corresponding age (hollow dots), taken from Davies and Shock [*17*]. The means and standard deviations of distribution are shown for each gouty and non-gouty group. The numbers in parentheses indicate the number of subjects in each age group. (The data from Davies and Shock refer to $C_{diodrast}$.)

The distribution of plasma urate levels in 150 gouty subjects (Table I) is indicated in Table II. The range is 5.3 to 13.7 mg. per cent, mean 9.0 ± 1.4 mg. per cent. It should be noted that these values reflect more or less decline resulting from the dietary restriction imposed prior to study (*cf. 20*); this, in five instances, resulted in plasma urate levels below 6.5 mg. per cent, our arbitrarily defined lower limit of hyperuricemia by the analytic method employed. In fifteen instances the serum urate level persisted in excess of 11 mg. per cent despite the dietary restriction.

The distribution of the figures for filtered urate load in these 150 gouty subjects is indicated in Table II. The range is 4.4 to 17.6 mg./minute, mean 10.1 ± 2.8 mg./minute. (Table I.) In a similar study based on one-hour urate and creatinine clearance measurements in sixty-four addi-

TABLE II

RELATION OF PLASMA URATE LEVEL TO FILTERED URATE LOAD IN 150 GOUTY SUBJECTS

Plasma Urate (mg. %)	No. Cases	Filtered Urate Load (mg./min.)								
		4.4–5.9	6.0–7.4	7.5–8.9	9.0–10.4	10.5–11.9	12.0–13.4	13.5–14.9	15.0–16.4	16.5–17.6
5.3–5.9	2	1	1	..	..	..	..	..	..	..
6.0–6.9	6	2	3	1	..	..	..	..	..	..
7.0–7.9	24	3	4	5	9	2	1	..	..	..
8.0–8.9	44	3	7	7	10	10	4	2	1	..
9.0–9.9	37	1	2	10	7	4	5	8	..	..
10.0–10.9	22	..	..	3	5	3	5	3	2	1
11.0–11.9	11	..	1	2	1	2	1	2	1	1
12.0–13.7	4	..	..	..	1	1	1	1	..	..
Total	150	10	18	28	33	22	17	16	4	2

tional gouty subjects the mean estimated filtered urate load was 11.6 mg./minute.

The substantial elevation of the plasma urate in these patients, combined with a relatively minor decline in glomerular filtration rate, as is characteristic of uncomplicated gout, thus results in a general increase in the filtered urate load, more pronounced in patients with serum urate levels above 8 mg. per cent. (Table II.) In 55 per cent of the 150 gouty subjects included in Table I the filtered urate load was in excess of 9.5 mg./minute (2 standard deviations above the normal mean); in twenty-one others it was in the range of 13.0 to 14.9 mg./minute and in seven the filtered urate load was in excess of 15 mg./minute. A similar distribution was obtained in the series of sixty-four additional gouty subjects. In both series, a filtered urate load within the low normal range, despite increased plasma urate levels, was usually associated with advanced age or systemic vascular disease presumed to affect the renal vasculature and resulting in a substantially reduced glomerular filtration rate.

Rate of urinary urate excretion: UV_{urate} in sixty-one non-gouty adult males, average age forty-one years, varied from 239 to 875 μg./minute, mean 493 $\pm$ 159 μg./minute. In 150 gouty subjects the range of UV_{urate} was much wider, 245 to 1657 μg./minute, mean 663 $\pm$ 235 μg./minute. The distribution of these values is indicated in Table III. It is evident that UV_{urate} in most cases (78 per cent) was within 2 standard deviations of the normal mean, varying from 200 to 800/μg./minute. The distribution is distinctly skewed however; in the balance of cases, 22 per cent, UV_{urate} was greater than 800 μg./minute—the rate of urinary excretion of urate in these instances was unequivocally in excess of the normal.

The data in twelve non-gouty and 150 gouty subjects, all studied by standard clearance technics, are plotted in Figure 6. There are 57 points representing gouty subjects whose filtered urate load was within the range of the mean ± 2 standard deviations (3.5 to 9.3 mg./minute) since, despite elevated serum urate levels, their glomerular filtration was markedly reduced—about one-third of these patients had overt renal damage. Their UV_{urate} too was almost invariably within the limits of the normal mean ± 2 standard deviations (303 to 791 μg./minute). In most of the gouty patients with filtered urate loads somewhat in excess of this range, UV_{urate} also was within normal limits but when the filtered urate load presented to the tubules rose beyond 10 mg./minute an increasing number of patients excreted excessive quantities of urate.

The relation of P_{urate} to UV_{urate} (Table III) is of interest in this connection. Considering the data in Table III as a whole, the correlation is not statistically significant. However, if the heterogeneous case material is segregated into appropriate groupings, it is possible to discern certain relationships. Thus it will be noted in Table III that of thirty-three patients whose rate of urinary urate excretion was excessive (>800 μg./minute) only two (6 per cent) had a plasma urate level less than 8 mg. per cent, as compared with 21 per cent below 8 mg. per cent for the

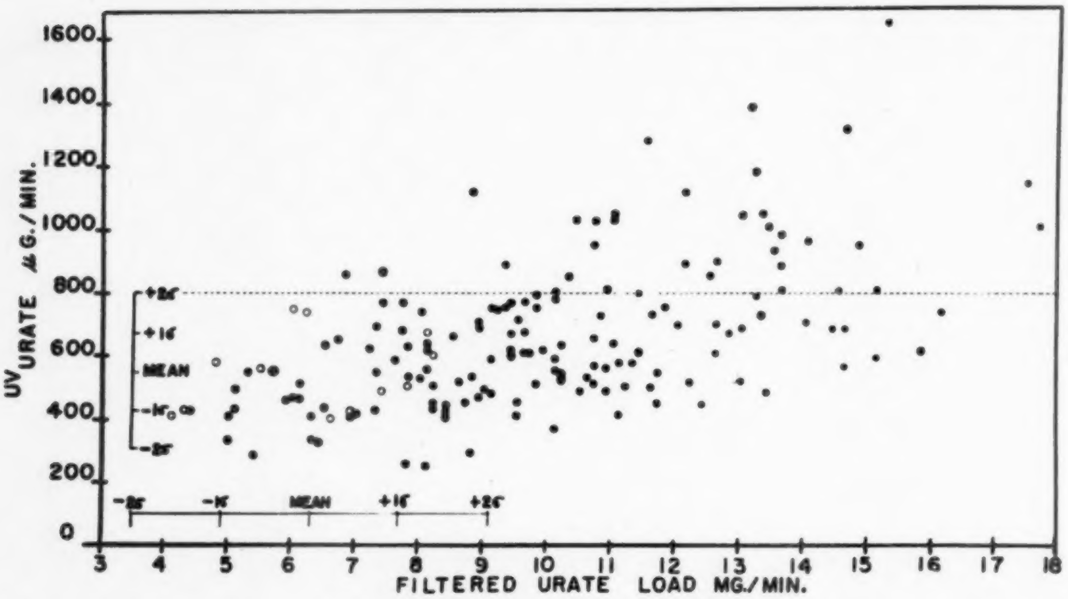

FIG. 6. Relation of UV_{urate} to filtered urate load in twelve non-gouty (hollow dots) and 150 gouty subjects (solid dots). The normal means ±2 standard deviations of distribution are indicated. The broken line at 800 µg./minute indicates the normal mean UV_{urate} + 2 standard deviations of distribution.

150 gouty subjects as a whole. The mean plasma urate level of the thirty-three patients in question was 10.2 mg. per cent, that of the remaining 117 cases 8.7 mg. per cent. At the other end of the scale, there were seven subjects, for the most part with overt renal damage, whose UV_{urate} was less than 350 µg./minute; the mean plasma urate level in this group was 8.2 mg. per cent.

Presumptive tubular reabsorption of urate: Assuming no tubular secretion of urate (an assumption which may require later modification), the quantity of filtered urate reabsorbed by the tubules may be equated to that amount which is filtered but not excreted. In twelve non-gouty adult males, the urate reabsorbed was calculated from standard clearance data to range from 3.7 to 7.6 mg./minute, mean 5.8 ± 1.4 mg./minute. In forty-nine non-gouty adult males, in whom one-hour urate and creatinine measurements were made, the mean was 6.2 ± 1.4 mg./minute.

Tubular reabsorption of urate, T_{urate}, was estimated in 150 gouty subjects studied by standard clearance technics. (Table I.) The figures

TABLE III

RELATION OF PLASMA URATE LEVEL TO UV_{urate} IN 150 GOUTY SUBJECTS

Plasma Urate (mg. %)	No. Cases	UV_{urate} (µg./min.)								
		245–349	350–499	500–649	650–799	800–949	950–1099	1100–1249	1250–1399	1400–1657
5.3–5.9	3	..	1	1	1	..	..	..	..	..
6.0–6.9	6	1	1	2	1	1	..	..	..	..
7.0–7.9	23	1	9	6	6	1	..	..	..	..
8.0–8.9	45	4	10	19	9	2	1	..	..	..
9.0–9.9	38	1	6	8	12	5	4	1	1	..
10.0–10.9	21	..	4	6	3	2	3	3	..	..
11.0–11.9	10	..	..	2	2	..	4	..	1	1
12.0–13.7	4	..	..	1	..	1	1	..	1	..
Total	150	7	31	45	34	12	13	4	3	1

indicate wide variation, from 4.0 to 16.6 mg./minute, with a mean of 9.5 ± 2.6 mg./minute. The distribution of these data is shown in Figure 7.

Figure 8 clearly demonstrates that, within the limits of filtered urate load encountered in our gouty subjects, the magnitude of urate reabsorbed by the tubules is a linear function of the magnitude of the filtered urate load presented to the tubules. It will be noted that the distribution of points representing gouty subjects, in the normal range of filtered urate load, is not discernibly different from that of the points representing non-gouty subjects.

The Urate Clearance. C_{urate} was estimated in forty-nine non-gouty men by one-hour urate and creatinine measurements and in twelve non-gouty men in the course of standard clearance procedures. The mean C_{urate} in these sixty-one non-gouty males was 8.7 ± 2.5 ml./minute, range 4.1 to 15.1 ml./minute. (The mean C_{urate} of fifty-two non-gouty females was 9.2 ± 2.7 ml./minute, range 4.4 to 16.5 ml./minute.) In sixty-four male gouty subjects the mean C_{urate} obtained by one-hour urate and creatinine measurements was 7.1 ± 1.5 ml./minute, range 2.8 to 13.9 ml./minute. In 150 male gouty subjects studied by standard clearance technics (Table I) the mean C_{urate} was found to be 7.5 ± 2.4 ml./minute, range 2.8 to 14.4 ml./minute. The distribution of the combined data for C_{urate} in the 214 gouty patients is illustrated in Figure 9 which indicates a spread almost in its entirety within 2 standard deviations of the normal mean.

The clearance of urate is calculated by the expression UV_{urate}/P_{urate} and it therefore is the resultant of multiple factors which in gouty

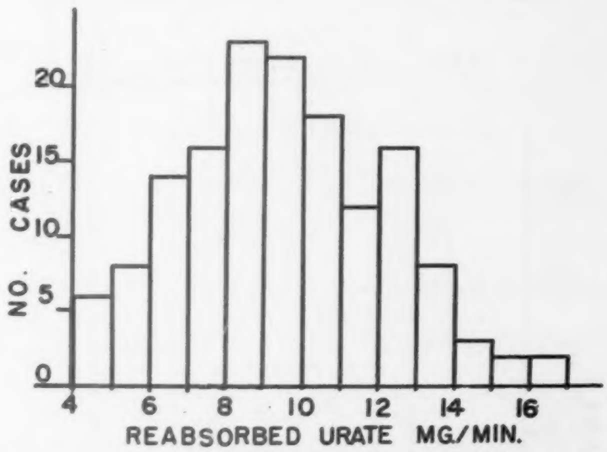

FIG. 7. Distribution of magnitude of urate reabsorbed by the tubules, mg./minute, in 150 gouty subjects.

subjects interact in particularly complex relationships. Some of these factors have already been discussed in connection with UV_{urate} and its relation to the filtered urate load (i.e., glomerular filtration rate and plasma urate concentration) and to tubular reabsorption of urate. The marked variations in the level of P_{urate} in gout often are critical in determining C_{urate}. Thus when P_{urate} is unusually high (>10 mg. per

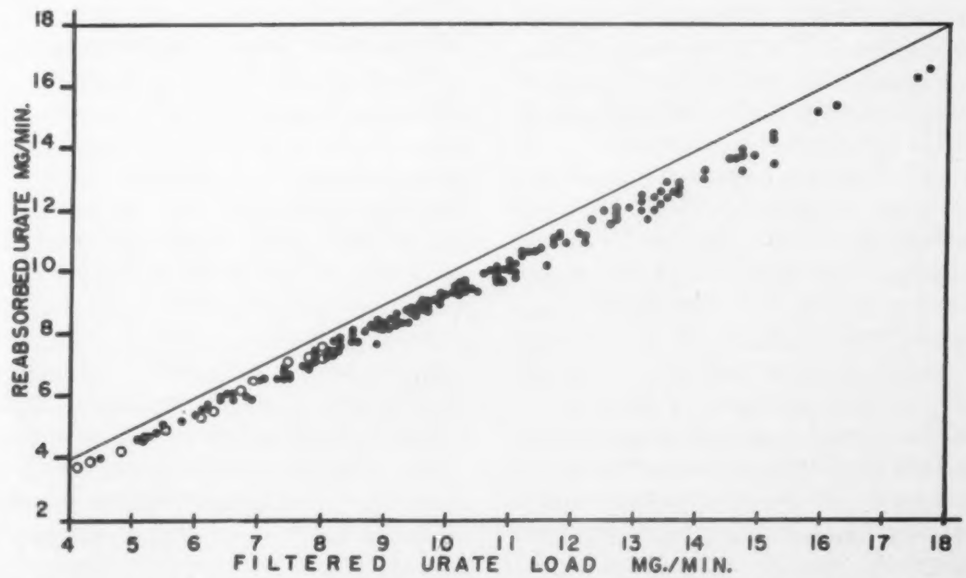

FIG. 8. Relation of urate reabsorbed by the tubules, mg./minute, to filtered urate load in twelve non-gouty (open circles) and 150 gouty subjects (heavy circles). The diagonal line indicates 100 per cent reabsorption.

cent), C_{urate} may be low; but if UV_{urate} also is very high, as usually occurs under these circumstances, C_{urate} exceeds or approximates the mean normal C_{urate} value. When P_{urate} is but little or only moderately elevated above the normal, UV_{urate} is apt to be within the normal range of variation; consequently C_{urate} is usually within the lower limits of normal variation.

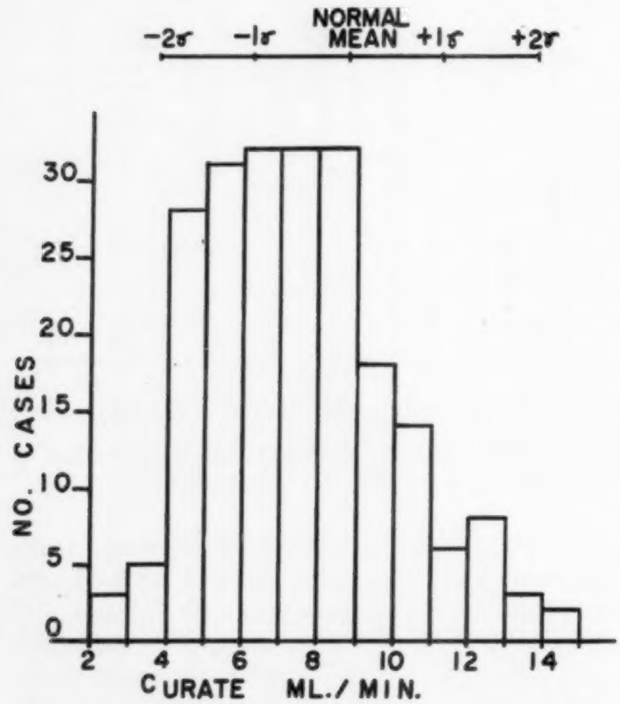

FIG. 9. Distribution of C_{urate} in 214 gouty subjects, in relation to the normal mean ±2 standard deviations of distribution.

C_{urate}/C_{inulin} Ratios. The mean C_{urate}/C_{inulin} (or $C_{urate}/C_{creatinine}$), expressed in percentage, of the sixty-one non-gouty males referred to in connection with the urate clearance was 7.6 ± 2.4 per cent. In 150 gouty subjects the mean was 6.8 ± 2.1 per cent, range 3.0 to 12.7 per cent. The distribution of values for the clearance ratios was similar, although shifted downward somewhat, to that shown in Figure 9 for C_{urate}, as anticipated in view of the previous discussion of inulin clearances in these patients. Again, the overlap with the normal limits of variation is marked, and the spread is almost in its entirety within 2 standard deviations of the normal mean.

If it be assumed that no tubular excretion of urate occurs, the C_{urate}/C_{inulin} ratio expresses the percentage of filtered urate load which is excreted. The quantity, $1 - C_{urate}/C_{inulin}$, would then indicate the percentage of filtered urate load which is reabsorbed. In sixty-one non-gouty subjects the mean figure so calculated was 91.9 ± 2.3 per cent, range 87.5 to 96.0 per cent. In 150 gouty subjects the mean was 93.1 ± 2.0 per cent, range 87.3 to 97.0 per cent. The distribution (Fig. 10) shows marked overlap within 2 standard deviations of the normal mean, with a skew toward higher percentages of reabsorption; the difference from the normal distribution, however, is not statistically significant ($p > 0.7$). A plot of $1 - C_{urate}/C_{inulin}$ against the filtered urate load failed to disclose any distinct trend in percentage urate reabsorbed as the filtered urate loads increased. This conclusion may be inferred from Figure 8.

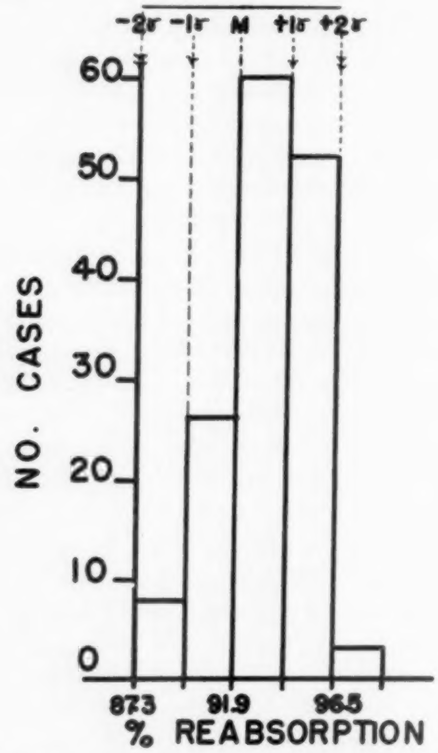

FIG. 10. Distribution of per cent of filtered urate load reabsorbed by the tubules in 150 gouty subjects, in relation to the normal mean ±2 standard deviations of distribution.

Twenty-four Hour Urinary Urate Excretion. The rate of urinary urate excretion, UV_{urate}, has already been considered in connection with urine collections of about one hour, in the course of clearance measurements. The data on twenty-four-hour urine collections, which include the period of nocturnal decline in urinary urate excretion, are in good general agreement. Additional points of interest, however, are brought out.

The mean twenty-four-hour urinary urate excretion in sixteen normal adult men, average

TABLE IV
URINARY URATE EXCRETION IN NORMAL SUBJECTS

Investigator	Subjects (no., sex, age)	Diet	Urinary Urate (mg./24 hr.)		Analytic Method
			Range	Mean	
Folin, Berglund, Derick (1924) [4]	6, M, 25–36	Meat-free low purine	425–605	509	Colorimetric (Folin method)
Brøchner-Mortensen (1940) [21]	8, M, 14–60 12, F, 15–50	Meat-free purine-free	269–532 293–477	374 374	Ferricyanide and iodometric titration
Friedman, Byers (1950) [7]	6, M, 23–36	Purine-free	360–438	390	Not specified
Gutman, Yü (1952) [9]	13, M, 30–63	Meat-free, low purine	360–438	416 ± 68	Colorimetric (modified Buchanan-Block-Christman method)
Crone, Lassen (1956) [22]	53, M, 18, F	Low purine	....	401 ± 42 321 ± 34	Ultraviolet spectrophotometry (Praetorius method)
Dubbs, Davis, Adams (1956) [23]	10	Low purine	....	583 ± 81	Ultraviolet spectrophotometry (modified Praetorius method)
Sandberg, Cartwright, Wintrobe (1956) [24]	10, M, 7, F	Low purine	320–460 276–435	410 383	Ultraviolet spectrophotometry (Praetorius method)

age forty-six years, was 418 ± 70 mg. The range was 308 to 533 mg./twenty-four hours. These values are in general accord with the collective data in the literature. (Table IV.)

The mean urinary urate excretion of 300 subjects with overt gout (average age, fifty years) was 497 mg./twenty-four hours. The range, 190 to 1520 mg./twenty-four hours, was strikingly wide. The distribution (Fig. 11) indicates that, in conformity with previous reports, the twenty-four-hour urinary urate excretion in most gouty subjects is within the normal range—200 cases (67 per cent) fall within the range 278 to 558 mg./twenty-four hours, or 2 standard deviations beyond the normal mean—and there are a few cases (thirteen or 4.3 per cent) in which excretion is less than normal (range 190 to 278 mg.). However, there is a marked skew in the distribution curve to the right. In eighty-seven cases (29 per cent) the twenty-four-hour urinary excretion exceeded 558 mg., our normal mean plus 2 standard deviations, and in fifty-four cases (18 per cent) it exceeded 628 mg., our normal mean plus 3 standard deviations.

It is apparent that, while the magnitude of urinary urate excretion in most patients with gout is within the rather broad limits of normal variation, unequivocally excessive urate excretion occurs in a sufficiently large minority to make up a significant segment of the whole—this is not an occasional anomaly. Analysis of the characteristics of these "overexcretors" which, for the purpose of discussion we shall limit arbitrarily and perhaps too conservatively to the fifty-four most striking cases, is of interest. The group included conspicuously few patients, four of fifty-four, with overt renal damage. (Fig. 9.) They were, for the most part, in the relatively younger age periods, averaging forty-five years as against fifty-one years in the remaining 246 patients. There was much overlap in this respect, however, as Table V demonstrates; it is an oversimplification to relate the magnitude of urinary urate excretion solely to the age of the patient. An occasional younger gouty patient has a fulminating course with precocious development of impaired renal function, or unrelated renal lesions may develop; on the other hand, most gouty subjects maintain good renal function until late in life. The serum urate level tended to be high (mean of 54 overexcretors, 9.8 mg. per cent; mean of 246 others, 9.0 mg. per cent). In the overexcretors the mean duration of manifest gout at the time of study was 9.7 years, as compared with 8.3 years in the remaining 246 cases. This difference was related to earlier onset of overt disease, i.e., acute gouty arthritis (mean age at onset in 54 overexcretors, thirty-five years; mean age at onset in the remaining patients, forty-one years). There was a lower incidence

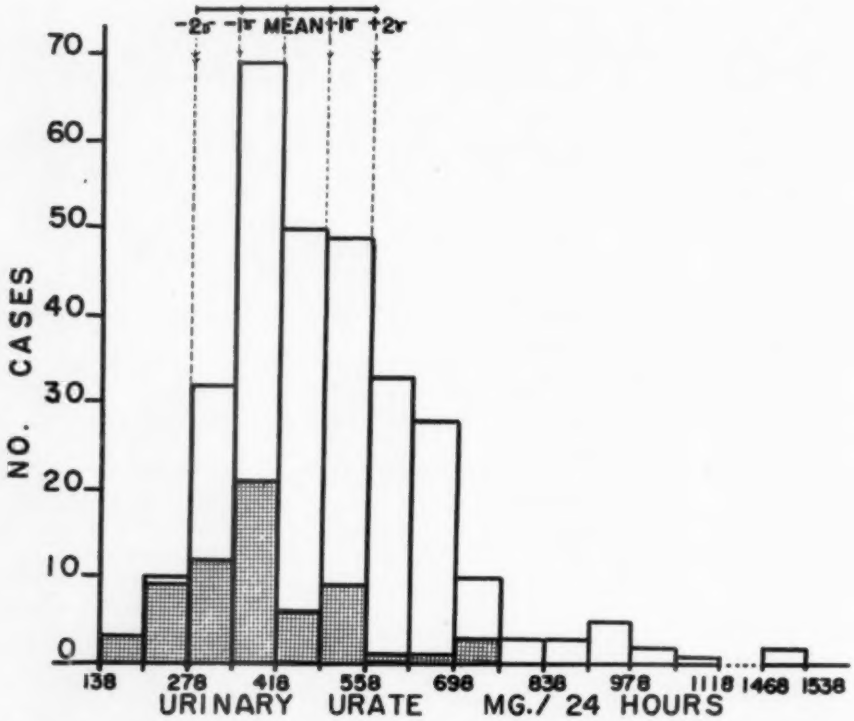

FIG. 11. Distribution of urinary urate excretion, mg./24 hours, in 300 gouty subjects, in relation to the normal mean ±2 standard deviations of distribution. The incidence of overt renal damage, as defined in the text, is indicated by cross-hatching.

of visible tophi in the 54 overexcretors, 38 per cent, as opposed to 48 per cent in the other 246 cases, and the magnitude of obvious tophaceous deposit was distinctly less; this presumably was related to the larger quantities of urate excreted.

TABLE V
AGE DISTRIBUTION OF FIFTY-FOUR "OVEREXCRETORS"
(Twenty-four-hour urinary urate excretion > 628 mg. or 3 standard deviations above the normal mean)

Age (yr.)	No. Cases	Urinary Urate Excretion (mg./24 hr.)				
		628–699	700–799	800–899	900–999	1000–1520
25–29	1	1	0	0	0	0
30–39	14	5	1	2	3	3
40–49	24	14	6	2	1	1
50–59	11	7	3	0	1	0
60–69	4	1	2	0	1	0
Total	54	28	12	4	6	4

Considering now the patients at the other extreme of urinary urate excretion, those whose output was low, analysis of the data emphasizes the critical significance of superimposed renal damage. Of the 300 gouty subjects, sixty-five gave evidence of kidney damage by the routine tests previously indicated. The mean twenty-four-hour urinary urate excretion in these sixty-five patients was 392 mg. (range 190 to 751 mg./twenty-four hours), as compared with a mean of 526 mg./twenty-four hours in the remaining 235 gouty subjects. Although comprising only about 20 per cent of the total number of patients, the sixty-five cases in question made up 40 per cent of the patients who excreted less than the mean normal figure of 418 mg./twenty-four hours, and only 11 per cent of the 186 patients who excreted more than the mean normal figure. Of the thirteen patients excreting less than 278 mg. urate/twenty-four hours (the mean normal figure minus 2 standard deviations) all but one had overt renal damage, including all three of the patients in the lowest category (190, 194 and 204 mg./twenty-four hours, respectively). Eight of these thirteen patients were over sixty years of age (mean age, sixty-six years; range fifty-three to seventy-eight years) and most of them had indication of vascular disease such as hypertension or myocardial infarction.

Of interest is the relationship of renal damage to the development of tophi. Of the 235 patients free of overt renal damage some 33 per cent exhibited tophi, whereas tophi were present in

71 per cent of the patients with renal damage, one-third of the latter group having extensive tophaceous deposits. Figure 12 brings out the point that after the age of fifty the incidence of tophi is significantly greater when renal damage is present than when it is absent.

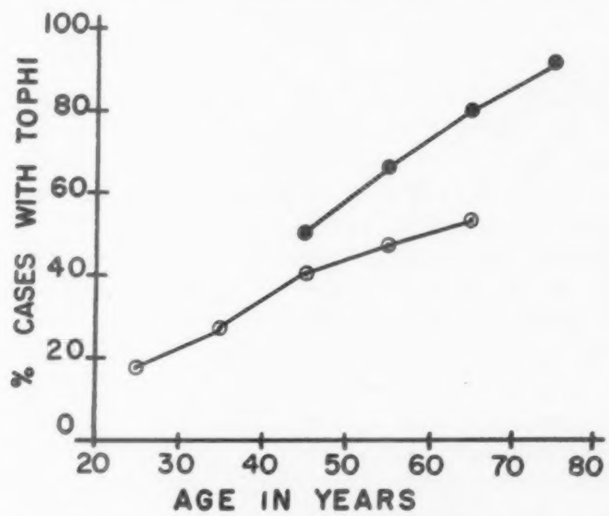

FIG. 12. Relation of incidence of visible tophaceous deposits to age in sixty-five gouty subjects with overt renal damage (solid dots), and 235 gouty subjects without apparent renal damage (hollow dots).

Decline in Twenty-four-Hour Urinary Urate Excretion in Patients under Observation for Long Periods. The foregoing observations suggest, what has long been suspected, that with deterioration of renal function as a result of age and/or disease the daily output of urate in gouty subjects is apt to decline. In exceptional instances this may be perceptible over relatively short periods, three to six years, and we have been able to document such a progressive course in a few cases. The observed decrease occasionally was sufficient to reduce the urinary urate excretion from unequivocally excessive to within the upper limits of normal variation, or from within the upper limits to within or below the lower limits of the normal range. In some but not in all instances this decline could be clearly related to the appearance or progress of overt renal damage. The following cases are illustrative.

H. G. when first seen at age thirty-nine had had recurrent acute gouty arthritis for fourteen years but tophi had not developed. No renal abnormality could be demonstrated then or since by any of the criteria employed, including repeated clearance studies. Yet his urinary excretion of urate, while on a basal diet, fell progressively from a mean of 972 mg./twenty-four hours at age thirty-nine to a mean of 695 mg./twenty-four hours at age forty-four; the mean serum urate level, initially 10.5 mg. per cent, remained essentially unchanged at a level of 10.8 mg. per cent. During this time tophi began to appear, indicating an increasing tissue urate pool. Urate biosynthesis continued at the same (excessive) rate, as shown by

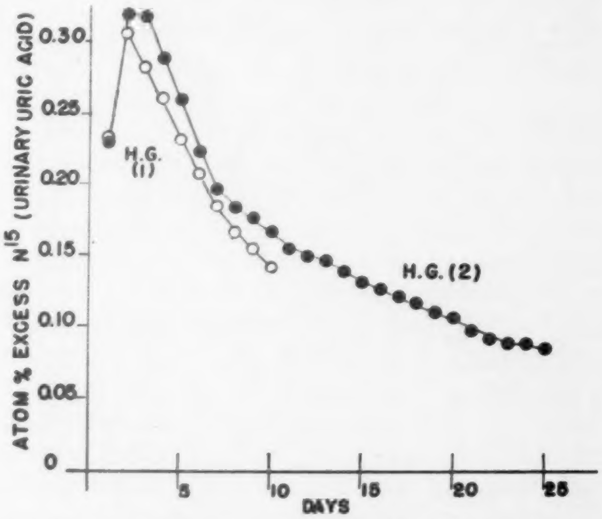

FIG. 13. Rate of incorporation of glycine N^{15} (100 mg./kg. body weight, in a single oral dose) into urinary urate in H. G. Hollow dots, October, 1951 [*70*]; solid dots, January, 1957.

repeated measurements of glycine-N^{15} incorporation into urate (Fig. 13), thus demonstrating that the fall in urinary urate excretion was not due to any decline in the magnitude of urate formation.

S. T. gave a long history of recurrent acute gouty seizures. When first seen at age forty-two he had for years had essential hypertension (blood pressure 160/100 mm. Hg) and presented with renal damage attributable to arteriolosclerosis and/or pyelonephritis secondary to repeated attacks of nephrolithiasis. There was 2 plus proteinuria and cylindruria with occasional red and white blood cells in the urinary sediment; the serum non-protein nitrogen was 42 mg. per cent; urinary concentrating power was impaired, phenolsulfonphthalein excretion was delayed. Despite renal impairment he excreted an average of 700 mg. urate/twenty-four hours while taking a low purine, meat-free diet. The serum urate was 12.7 mg. per cent. Extensive tophi were present; these responded slowly to uricosuric therapy which increased the urinary urate output to about 1,000 mg./twenty-four hours. At age forty-five his manifestations of gout were much improved but the hypertension had increased to 180/120 mm. Hg. Although the criteria of renal damage were not appreciably worsened, the urinary urate excretion, months after withdrawal of uricosuric drugs, had fallen to a mean of 444 mg./twenty-four hours. The mean serum urate level had increased to 14.3 mg. per cent.

TABLE VI

RESULTS OF RENAL CLEARANCE STUDIES IN THIRTEEN HYPERURICEMIC MEMBERS OF GOUTY FAMILIES
(Arranged in descending order of filtered urate load, F_{urate}. Values not corrected to standard body surface area)

No.	Age (yr.), Sex	Body Surface Area (sq. meter)	P_{urate} (mg. %)	C_{inulin} or $C_{creatinine}$ (ml./min.)	C_{PAH} (ml./min.)	F_{urate} (mg./min.)	UV_{urate} (µg./min.)	T_{urate} (mg./min.)	C_{urate} (ml./min.)	Urinary Urate (mg./24 hr.)
1.	21, M	1.82	10.3	131*	...	13.5	640	12.9	6.2	655
2.	17, M	2.00	9.9	135	735	13.4	690	12.7	7.0	660
3.	26, M	2.12	7.9	141	...	11.4	579	10.8	7.4	...
4.†	17, M	1.96	6.2	182	799	11.3	755	10.5	12.2	461
5.	18, M	2.01	7.0	146	...	10.2	457	9.7	6.6	...
6.	18, M	2.17	7.2	142	840	10.2	620	9.6	8.6	...
7.†	20, M	1.86	6.4	158	693	10.1	570	9.5	8.9	548
8.‡	45, M	2.04	7.8	108*	...	9.8	618	9.2	7.9	...
9.	29, M	1.85	7.9	112*	...	8.9	510	8.4	6.5	...
10.	30, M	1.88	6.5	135	...	8.8	538	8.3	8.3	472
11.	32, M	1.83	5.9	145*	...	8.6	439	8.2	7.4	...
12.	27, F	1.50	6.8	95.9*	...	6.5	355	6.1	5.2	...
13.‡	40, F	1.80	5.8	100*	...	5.8	670	5.1	11.6	...

* $C_{creatinine}$. †, ‡ = siblings.

J. L., long subject to recurrent acute gouty attacks, gave no evidence of renal damage when first seen at the age of fifty-five. His phenolsulfonphthalein excretion was 67 per cent in two hours and the serum non-protein nitrogen was 31 mg. per cent. He excreted an average of 527 mg. urate/twenty-four hours, with a serum urate level of 9.8 mg. per cent, while taking a basal diet. Moderately extensive tophi were present. While prophylactic colchicine controlled the acute gouty attacks, he did not respond to large doses of uricosuric agents; the tophi remained unchanged. In the meantime, hypertension developed and his renal function became impaired. At age fifty-eight, renal clearance studies showed an inulin clearance of 69.5 ml./minute and the para-aminohippurate clearance was 293 ml./minute. The average urinary urate excretion had fallen to a mean of 424 mg./twenty-four hours, and the mean serum urate level had risen to 11.5 mg. per cent.

Renal Regulation of Urate Excretion in Hyperuricemic Members of Gouty Families. In order to study the earliest recognizable phase of the gouty trait, renal clearances were measured in thirteen hyperuricemic members of eleven gouty families;* none had yet suffered an attack of acute gouty arthritis. Four male subjects were still in their teens, not long past puberty when hyperuricemia in the male usually first appears [25].

The data are summarized in Table VI. C_{inulin} (or $C_{creatinine}$) and C_{PAH}, when corrected to standard body surface area, were for the most part within the limits of normal variation for the age groups represented. The filtered urate load, in consequence of the elevated plasma urate level and normal glomerular filtration rate, was in excess of the normal mean in all of the eleven males. T_{urate} was correspondingly but not disproportionately high. The UV_{urate} varied from 439 to 755 µg./minute in the eleven males, with a mean of 583 ± 90 µg./minute; higher than the mean of non-gouty subjects (493 ± 159 µg./minute) but lower than that of our series of 150 patients with manifest gout (663 ± 235 µg./minute). The twenty-four-hour urinary urate excretion exceeded 628 mg. (the normal mean plus 3 standard deviations) in two of five instances—they may be classified as unequivocal overexcretors. C_{urate} varied from 6.2 to 12.2 ml./minute in the eleven males.

COMMENTS

Renal Regulation of Urate Excretion in Normal Man. It appears now to be generally accepted that the plasma urate is virtually wholly filtrable at the glomerulus and that the filtered urate load

* In three subjects (Cases 4, 7 and 11) the plasma turate at the time of studyhad declined somewhat below heir usual hyperuricemic level in response to prior dietary restriction.

may be taken to be the product of the glomerular filtration rate and the plasma urate concentration. In normal adult man the filtered urate load is thus calculated to be of the order of 6 or 7 mg./minute. About 0.5 mg. urate/minute is excreted in the urine. The deficit, which appears to be approximately 92 per cent of the filtered urate, is attributable to reabsorption in the tubules.

If the filtered urate load is increased in normal man by intravenous infusion of urate, tubular reabsorption of urate increases *pari passu* until a maximum rate of reabsorption is reached, beyond which no significant reabsorption occurs with further increase in the filtered load [*26*]. This pattern indicates that tubular reabsorption of urate is effected by an "active" process of limited capacity, presumably enzymatic. The mean Tm_{urate} in normal man has been estimated by Berliner et al. [*26*] to be of the order 15 mg./minute/1.73 M^2 body surface area. The nature of the transport mechanism for tubular reabsorption of urate has not been further elucidated.

It is curious that uric acid, a metabolic end-product of no apparent utility, should be so sedulously conserved by renal tubular reabsorption in man, who possesses no uricase. Perhaps this is an evolutionary vestige, since reabsorption of urate in most mammals presumably is for the purpose of conversion to allantoin. However, it must be remembered that if urate were not very largely reabsorbed, the concentration of urate in the urine would be such as to make calculus formation inevitable.

It is apparent that excretion of urate normally occurs at filtered urate loads far smaller than the tubular capacity for reabsorption of urate. Consequently, as Berliner et al. [*26*] pointed out, the Tm_{urate} *per se* cannot be considered to determine, at least directly, the magnitude of urate excretion. The nature of the immediate excretory mechanism remains obscure.

Renal Regulation of Urate Excretion in Gout. The plasma urate in the hyperuricemia of gout also is virtually wholly filtrable [*19*], and the filtered urate load again may be assumed to be equivalent to the product of the inulin clearance and the plasma urate concentration. The inulin clearance in gouty subjects is apt to be somewhat reduced, for the most part commensurate with their age but sometimes more markedly because of the presence of renal vascular disease unrelated or related to gout. The elevation of plasma urate, however, usually is such that the filtered urate load in most cases exceeds the upper limit of normal variation. In the present study of 150 cases by standard clearance technics the mean C_{inulin} was 98.5 ± 17.7 ml./minute (corrected to standard body surface area), the mean plasma urate was 9.0 ± 1.4 mg. per cent, and the mean filtered urate load was 10.1 ± 2.8 mg./minute, with a broad range of variation from 4.4 mg./minute to as high as 17.6 mg./minute. (The filtered urate loads were calculated from uncorrected inulin clearances.)

The tubular reabsorption of urate in gouty subjects, in the face of these increases in filtered urate loads, may be compared with the tubular reabsorption of urate in normal human subjects in whom the filtered urate load has been artificially augmented by intravenous infusion of urate. (In the experiments in normal man [*26*], successive points on the titration curve of increasing filtered urate loads were obtained in individual subjects by sustained infusion; in the observations on gouty patients, each patient represents a single point in a collective ascending "titration curve" comprising many patients.) In gouty subjects, as in normal subjects, the tubular reabsorption of urate increases directly with increase in the filtered urate load, and apparently in the same degree. (Table I, Fig. 8.) There is no indication in Figure 8 of a flattening out of the urate reabsorption curve even at the highest filtered urate loads encountered (up to 17.6 mg./minute); i.e., no clear evidence of complete saturation of the tubular reabsorptive capacity for urate in these cases, the Tm_{urate} was not reached. As in normal subjects [*26*], there appears to be slightly more splay in the higher ranges of the "titration curve," attributable to disparity in "glomerular-tubular balance" [*18*].

In contrast to the regular relation of T_{urate} to F_{urate}, the relation of excreted urate (whether measured as UV_{urate} in short clearance experiments or as twenty-four-hour urine collections) to the filtered urate load is unpredictable. (Table I, Fig. 6.) For the most part, there was striking independence of these two quantities (Fig. 6), UV_{urate} remaining within the bounds of the normal mean ±2 standard deviations over a wide range of filtered urate load. However, when excessive urinary urate excretion (the incidence and significance of which already has been commented upon) did occur, it was associated, in general, with inordinately high plasma urate levels and abnormally large filtered urate loads. Relatively low filtered urate loads

were associated for the most part with relatively low or reduced urinary excretion of urate.

The measurable parameters of renal function in gouty subjects, notably in their younger years but also often with advancing age, are usually commensurate with those of their non-gouty fellows at the same time of life. However, there is some predisposition to renal disease which, as has long been appreciated, is an important cause of death in gout. In the present series of 300 patients, sixty-five gave evidence of overt renal damage. The relation to age (and duration of disease) is indicated by the following incidence: overt renal damage was present in 92 per cent of those in the eighth decade, 40 per cent of those in the seventh, 24 per cent in the sixth, 10 per cent in the fifth, 2 per cent in the fourth and in none of those in the third decade. This predisposition to renal damage, and its age distribution, is readily understandable as related to the degenerative vascular changes of advancing years, arteriolosclerosis associated with hypertension, pyelonephritis resulting from calculus formation and infection, as well as to direct injury by cumulative urate deposits in and around the renal tubules and collecting system [*27–29*].

As Garrod [*30*] made clear, and others [*14,31*] have since emphasized, the most common indications of early renal damage in gout are inability to concentrate solids (and isosthenuria) and a trace of protein in the urine sometimes accompanied by a few granular casts; delay in excretion of phenolsulfonphthalein is a characteristic accompaniment. Many years later, proteinuria may become more abundant, the urine volume may decline and retention of urea may occur; these, as Garrod [*30*] recognized, are signs that portend poorly for the patient.

This sequence of events suggests that the early manifestations of renal impairment are due principally to tubular damage, referable to the tubular and interstitial urate deposits, and associated infection and vascular changes, found at necropsy [*27–29*]; the results of our clearance studies (Table I) are compatible with this interpretation. Later, however, in consequence of deterioration in the renal vasculature associated with aging and/or disease, the glomerular filtration rate begins to decline and the filtered urate load may be reduced. At this point renal retention of urate, and eventually of other non-protein nitrogen components, becomes apparent. Our data provide a sufficiency of evidence to support the view [*13*] that this increase in hyperuricemia is a consequence, not a primary cause of gout, complicating the ravages of age.

It is relevant in this connection to note that the incidence and severity of tophaceous deposit in older gouty patients with overt renal damage is significantly higher than in those apparently not so burdened. (Fig. 12.) This reflects accelerated expansion of the body pool of urate [*32*], what Garrod [*1*] referred to as "a vicarious discharge of urate of soda," which presumably occurs if renal retention of urate is superimposed upon overproduction of urate. Another possible avenue of vicarious discharge may be the gastrointestinal tract, the "enterotropic" excretory route, which normally is believed to account for 40 to 70 mg./day, or 10 to 15 per cent of the normal urinary urate excretion [*33*]. It is further possible that under these circumstances the limited uricolysis in man, estimated to account for about 25 per cent of the daily turnover of urate [*34*], may be augmented.

Role of Tubular Reabsorption of Urate in the Pathogenesis of Gout. Thannhauser [*35*] has suggested that the hyperuricemia and clinical manifestations of gout are due to an inborn error characterized by increased tubular reabsorption of uric acid; the error being compounded by man's innate lack of uricase to degrade the excessively reabsorbed urate. This proposal will be recognized as a restatement, in more modern terms, of Garrod's position [*1*].

The severe limitations of current clearance technics make proof or disproof of this view difficult. The magnitude of urate reabsorbed by the tubules is estimated indirectly, by difference, and involves subtraction of a small quantity (UV_{urate}) from a large quantity (the filtered urate load). Moreover, a slight increase in reabsorbed urate, far too small to be detected by clearance methods, would, in the course of time, markedly increase the plasma urate level and profoundly affect the course of gout; in fact, if sufficiently continued would, in due course, completely ossify the patient to one huge tophus!

Granting all this, the data do suggest certain conclusions which appear to rest upon a reasonable basis of probability. They indicate that the quantity of urate reabsorbed by the tubules in most gouty subjects is indeed greater than normal, in fact may be more than twice the amount. This, as already indicated, is due to the circumstance that the filtered urate load presented to the tubules usually is so much larger than in

normal man (unless receiving an intravenous infusion of urate); consequently, as in normal man, tubular reabsorption of urate is increased. When the filtered urate load is normal or even reduced, due to decrease in glomerular filtration rate, the quantity of urate reabsorbed in gouty subjects is in the normal range or somewhat reduced. (Fig. 8.) So far as can be determined, the percentage of filtered urate reabsorbed in gout appears not to be (statistically) significantly different from the normal, irrespective of whether the filtered urate load is high, normal or low. In short, the tubular response of the gouty subject seems not to be essentially different from that of normal man at equivalent filtered urate loads. The abnormality in gout, then, does not appear to reside in the activity of the tubules reabsorbing urate but in the filtered urate loads presented to them.

The high filtered urate loads of most gouty subjects are due to their high plasma urate concentrations but, unlike the intravenous urate infusion experiments of Berliner et al. in normal man [*26*], the "infusion" of urate in gouty subjects taking a basal diet must of course come from endogenous sources. The overproduction of urate by biosynthesis is thus implied. This has been unequivocally demonstrated, by isotope labeling experiments [*10,11*], to occur in the substantial minority of patients who maintain hyperuricemia despite excessive urinary excretion of urate. It has not yet been unequivocally demonstrated in those with a urinary urate output within the limits of normal variation. In such cases, to be sure, the specific activity of urate after administration of glycine-C^{14} in tracer doses, without a glycine load, may be greater than in the normal subject [*36*] but it is not as yet clearly established that this necessarily indicates overproduction of urate [*37*]. The hyperuricemia and occasional secondary gout associated with polycythemia [*38,39*], myeloid metaplasia [*39–41*], leukemia and related disorders have been shown to be associated with overproduction of urate and other purines in the course of accelerated turnover of nucleic acids.

Of course, preservation of the normal tubular reabsorptive activity in respect to urate, in the face of markedly increased filtered urate loads, helps to sustain the hyperuricemia of gout and in this regard is distinctly disadvantageous to the gouty patient.* However, unless the body pool of urate were constantly replenished at an excessive rate, the hyperuricemia would soon revert to normal levels, due to excretion of urate in the urine. This is what happens in the normal subject upon discontinuance of infusion of urate [*26*], and this is what may be presumed to occur in gouty subjects, even if tubular reabsorption of urate were excessive, unless the rate of urate production were greater than the rate of loss in the urine and by other routes.

The Question of Tubular Excretion of Urate. The preceding discussion is based on the prevailing premise that the tubules do not excrete urate. If tubular excretion of urate does, in fact, occur in normal and/or gouty subjects, all the calculated figures for tubular reabsorption of urate are too low. Under these circumstances the standard clearance technics employed would not permit comparison of the magnitude and percentage of the urate reabsorbed by the tubules in the normal and gouty subject, and there would be no point in worrying the available data. If, however, the excreted urate derives solely from tubular secretion, and tubular reabsorption of the filtered urate load is therefore complete in both normal and gouty subjects, it could hardly be argued that the hyperuricemia of gout is due to excessive tubular reabsorption of urate!

Prior investigators have suggested from time to time that in man, as in many lower forms, urate may be secreted by the tubules. This was first postulated on the general assumptions of the Heidenhain theory of tubular secretion and later on the supposition that the plasma urate is largely or wholly present as large molecular polymers or securely bound to plasma proteins, hence non-filtrable. This basis for postulation of tubular secretion of urate appears no longer to be tenable.

The question presently under consideration is whether or not the urate of the glomerular filtrate, assuming complete filtrability of the plasma urate, may not normally be virtually completely reabsorbed by the tubules (even more than the 90 or 95 per cent now conceded) and the excreted urate derived wholly or in very

* Since the presumptive overproduction of urate in the gouty patient is not amenable to control save inadequately by dietary restriction, uricosuric agents are administered to increase urinary excretion of urate by suppressing the normal percentage of filtered urate reabsorbed by the tubules to abnormally low levels. The favorable clinical response so obtained should not be construed as proof that the primary cause of gout is abnormally great tubular reabsorption of urate.

large part by tubular secretion. The excreted urate would also include filtered urate which has escaped reabsorption under conditions of deficient tubular reabsorption of urate, whether caused by uricosuric drugs, by disease (inborn or acquired), or by the possible circumstance of filtered urate loads in excess of the capacity of the healthy tubules fully to absorb them. The available clearance data, including our own, appear not to exclude tubular excretion of urate in man. On the other hand, direct evidence for it has not been adduced.

The immediate question arose in connection with the paradoxic retention of uric acid caused by uricosuric drugs, notably salicylate and phenylbutazone, in low dosage [*42*]. In the case of pyrazinamide and pyrazinoic acid this retention is so marked that the urinary excretion of urate is reduced to 5 or 10 per cent of the premedication output, without lowering of the inulin clearance [*43*]. These effects may well be brought about by enhanced tubular reabsorption of urate. They may also be the result of inhibition of a tubular excretory mechanism; in the latter event virtually complete tubular reabsorption of urate and tubular secretion of almost all the excreted urate would have to be postulated.

Further consideration of the possibility of tubular excretion of urate is appropriate to the present study because our data reveal a rather striking degree of independence of the renal excretory mechanism for urate under the wide range of variation in discrete renal functions exhibited by gouty subjects. The poor correlation between inulin clearance and urate excretion is noteworthy. (Table I.) When C_{inulin} is greater than 100 ml./minute the renal excretion of urate unpredictably may be excessive, within the normal range, or significantly less than normal; however, reduction of the glomerular filtration rate below 80 ml./minute was not associated with overexcretion of urate. The dissociation of C_{urate} and C_{inulin} in patients with severe renal disease was emphasized by Coombs et al. [*13*] and others, and is borne out by our experience. The unpredictability of UV_{urate} in relation to the filtered urate load and to the reabsorptive capacity of the tubules has already been commented upon. (In fact the only correlation which is at all significant is the usually conspicuous elevation in plasma urate level associated with excessive UV_{urate}.) This general dissociation is reminiscent of the circumstances of renal regulation of potassium excretion [*44,45*]. The filtered potassium, it is postulated [*45*], is completely reabsorbed by the tubules under physiologic conditions, the urinary potassium being derived wholly or in large part from tubular secretion, in this instance by exchange for sodium.

It may be proper in this connection to mention an early suggestion by Thannhauser [*46*], that the hyperuricemia and manifestations of gout may be due to a functional impairment in the secretion of uric acid by the renal tubules. At present, one can consider only the *a priori* probabilities of such an event. Presumably, if the genesis of hyperuricemia were ascribed to less than normal urinary excretion of urate, the hypothesis of deficient tubular excretion of urate would not apply to gouty subjects excreting excessive quantities of urate on a basal diet, or even to those with a urinary urate output within the normal range, unless overproduction of urate also were assumed. Reduced excretion of urate, however, occurs chiefly in gouty subjects with manifest renal damage and marked impairment in glomerular filtration rate, which presumably is largely responsible for the retention of urate.

General Considerations. If gout were the result simply of hyperuricemia due to excessive tubular reabsorption or deficient tubular secretion of urate, it should be no rarity when uric acid is retained because of reduced glomerular filtration, as in chronic glomerulonephritis. This brings us to the basic premise of every theory postulating renal retention of urate, by whatever mechanism, as the primary cause of gout: that all the complex manifestations of the disorder, including acute gouty arthritis, can be ascribed to uric acid, a virtually inert end-product of purine metabolism. True, the blinders of tradition have all too long circumscribed vision in this field to the narrow horizon offered by uric acid *per se*; and tophaceous deposit is indeed an indication that excretion of urate has not kept pace with biosynthesis. But when the composite syndrome of gout is fairly viewed, in broad perspective, it seems hardly possible to comprehend it as a consequence simply of hyperuricemia due to renal retention [*9*]. Some subtle, as yet obscure deviation of metabolism, more marked in some carriers of the gouty trait than in others, would seem more likely to be responsible. The recent isolation, from the urine of gouty subjects, of excessive quantities of 8-hydroxy-7-methylguanine and adeninesuccinic acid, sug-

gesting abnormalities in intermediary guanine and adenine nucleotide metabolism, respectively [*47,48*], may offer some clue to the nature of this metabolic error.

Conclusion. Which, then, came first, chicken or egg, hyperuricemia or renal retention of urate? We think hyperuricemia, one expression of an inborn error profoundly affecting some aspect of intermediary purine metabolism and leading to overproduction of urate.

SUMMARY

1. A study was made of renal function in some 300 gouty subjects. Standard renal clearance technics were employed in approximately 160 cases, including some asymptomatic hyperuricemic relatives of these gouty subjects.

2. C_{inulin}, C_{PAH} and Tm_{PAH} were for the most part consonant with the values found in normal subjects of equivalent age, but impairment of renal hemodynamics was not infrequent particularly in those of advanced age or with overt renal disease.

3. Determinations of urinary urate excretion, whether measured as UV_{urate} in short clearance experiments or in twenty-four-hour urine collections, gave values within the normal range in most cases. In a significant minority of instances, however, the urinary urate excretion was unequivocally in excess of the limits of normal variation.

4. The filtered urate load was found to be increased in most gouty subjects. The presumptive tubular reabsorption of urate was correspondingly increased but, so far as could be determined, not disproportionately so in relation to the percentage of urate reabsorbed by the tubules at equivalent filtered urate loads in normal man.

5. The results thus indicate essentially normal discrete renal functions in most gouty subjects. With advancing years and disease, however, the glomerular filtration rate progressively declines and some tubules apparently deteriorate. Secondary renal retention of urate then becomes apparent.

6. The data fail to disclose any primary defect in tubular function, specifically of abnormally enhanced tubular reabsorption of urate. On the contrary, the clearance data imply overproduction of urate in gout. This interpretation is supported by reference to metabolic data.

7. The question of tubular excretion of urate is reviewed. The available clearance data are not incompatible with the view that the filtered urate load, assuming complete filtrability of plasma urate, normally is wholly or in very large part reabsorbed by the tubules, and that the excreted urate derives entirely, or for the greater part, from tubular secretion; the analogy with potassium excretion is pointed out. Indirect but not direct support of this postulation is presented.

8. It is concluded that the pathogenesis of hyperuricemia and of the other manifestations of gout cannot be ascribed to any hypothetic primary renal defect, whether of abnormally great tubular reabsorption or deficient tubular secretion of urate.

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Review

Salt and Water Volume Receptors*

An Exercise in Physiologic Apologetics

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Salt and Water

In the beginning the abundance of the sea
Led to profligacy
The ascent through the brackish waters of the estuary
To the salt-poor lakes and ponds
Made immense demands
Upon the glands
Salt must be saved, water is free

In the never-ending struggle for security
Man's chiefest enemy,
According to the bard of Stratford on the Avon,
The banks were climbed and life established on dry land
Making the incredible demand
Upon another gland
That water, too, be saved.
Maurice B. Strauss [*142*], November 23, 1951.

THE subtitle of this paper is not an apology for adding one more document to an already word-weary subject; the term "apologetics" is used in the sense in which it has been applied to certain other literature, meaning the critical examination of the texts in an effort to establish what is, perhaps, only an *a priori* thesis, or to clarify that which is unclear, or to disentangle fact from fiction; and this, without introducing any new factual material whatever.

HISTORIC

As early as 1896 Starling [*130*], writing on dropsy, suggested that the failure of the kidneys to excrete salt led to hydremic plethora and to increased venous pressure, the latter in turn leading to dilatation and then to the ultimate failure of the already incompetent heart. His interpretation adumbrated the currently captious question of how much, if anything, the heart has to do with chronic congestive heart failure.

Again it was Starling [*129*] who seems to have first explicitly stated that the renal excretion of salt and water must be conditioned by the volume of the body fluids, as well as by their composition. "The kidney," he said, "presents in the highest degree the phenomenon of 'sensibility,' the power of reacting to various stimuli in a direction which is appropriate for the survival of the organism; a power of adaptation which almost gives one the idea that its component parts must be endowed with intelligence."

It is implicit in the principles of homeostasis, as developed by Walter Cannon [*23*], that when we observe a homeostatic state we are generally warranted in looking not only for an effector mechanism but also for receptor and possibly integrative mechanisms. What follows is largely compliance with Cannon's principles. Starling's

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exalted view of the wisdom of the kidney we must regretfully reject; the kidney appears to be only a passive agent operating blindly and automatically according to the dictates of receptor-effector systems located elsewhere in the body; the integration of these receptor-effector systems constitutes the wisdom behind salt and water balance.

John Peters in 1935 [*108*] suggested that one factor conditioning sodium excretion was some function of the volume of the circulating blood, and specifically some change in its distribution. Borst [*16*] considered that changes in the extracellular fluid volume operate to maintain the volume of circulating blood within narrow limits; but as for details we are given only the premise that an increase in blood volume leads to increased venous pressure and thus to increased cardiac output, the last somehow increasing salt and water excretion. Other writers have had recourse to decreased or increased cardiac output as a directly effective stimulus, but it is not clear how cardiac output *per se* can operate as a stimulus unless through pressure receptors, volume receptors or the net rate of oxygen delivery to, or accumulation of metabolites in, one or more organs of the body. Aside from this difficulty, during the pyrexial reaction the cardiac output is substantially increased (as is also the renal blood flow), but no increase in the excretion of sodium or water occurs [*87*].

Hence we may look with profit elsewhere for receptor systems sensitive to changes in body fluid volume and participating in salt and water balance.

SELECTION OF MATERIAL FOR REVIEW

Abundant evidence is available indicating that, tubular activity apparently remaining constant, the excretion of both sodium and water is conditioned by glomerular-tubular balance, although it is beyond the purview of this paper to review this evidence here. Moreover, it is well known that changes in filtration rate can readily be induced in the dog, less readily in man, by reversible physiologic procedures, but the means by which such changes are initiated by changes in body fluid volume and integrated with changes in tubular reabsorption remain to be examined. This discussion is concerned only with changes in specific tubular reabsorptive activity, and consequently the literature reviewed is confined as far as possible to circumstances in which changes in glomerular activity are absent, negligible in magnitude or on other grounds have been ruled out by the investigator as causally related to changes in excretion. (Admittedly a decision on this matter has sometimes been made rather arbitrarily.) It follows that, with few exceptions, it has been necessary to confine the discussion to studies in which the filtration rate has been measured, thus excluding many otherwise potentially valuable studies in both dog and man. Also excluded are all experiments involving the use of drugs, the interpretation of which is at this time so speculative that they contribute little to our immediate goal, and also preliminary abstracts in which the evidence cannot be examined.

More importantly, we have excluded all studies involving long-term experimental procedures or pathologic changes in the cardiovascular system or kidneys. Where multiple controls are superimposed on a function, such as sodium excretion, it is conceived that normal regulatory mechanisms may be obscured by compensatory reactions. Nor does it seem safe at this time to assume that all pathologic disturbances in sodium excretion (anemia, hypoproteinemia, constrictive pericarditis, constriction of pulmonary artery or hepatic vein, hepatic cirrhosis, nephrosis, chronic congestive cardiac failure, etc.) issue from excitation or failure of the same regulatory mechanism(s), or (as is frequently implied) that they represent compensatory reactions serving a physiologically useful end. Despite these exclusions, we are left with a rather large body of literature for consideration.

CELL SEPARATION THEORY

Pappenheimer and Kinter [*104*] and Kinter and Pappenheimer [*71,72*] have recently advanced evidence that plasma skimming may effect a substantial separation of plasma and cells in the postglomerular capillary circulation, and also possibly along the course of the lobular (interlobular) arteries. Insofar as plasma skimming occurs in the latter, the hematocrit of the blood perfusing the glomeruli at successive peripheral levels along the artery would be progressively increased, reducing the filtration fraction. The extent of cell-plasma separation will be determined by the mean perfusion pressure and the hematocrit of the arterial blood. Consequently, where either mean systemic pressure or hematocrit are abruptly changed, the volume of filtrate formed in glomeruli at various levels of the renal vascular tree may also be

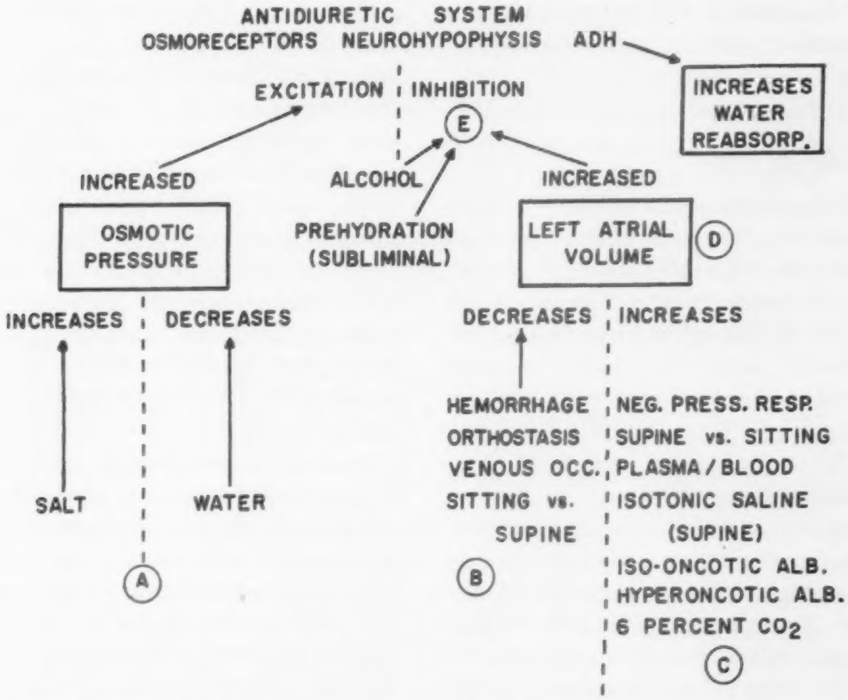

FIG. 1. Schema showing possible inter-relations between volume receptors and the antidiuretic system. The encircled letters supply reference points in the text.

changed, altering glomerular-tubular balance. Although the cell separation theory is of the utmost importance to renal physiology, nothing is known as yet concerning its application to sodium and water balance. It seems, however, that the interpretation of most of the studies reviewed here will not be markedly affected by changes in plasma skimming: for example, the natriuretic effects of the infusion of large volumes of saline solution are in part controlled by the absence of natriuresis after the infusion of iso-oncotic albumin and the antinatriuretic effects of hyperoncotic albumin solutions. However, we cannot exclude variations in the renal distribution of cells and plasma as factors contributing to changes in water and sodium excretion in experiments in which arterial pressure or hematocrit are substantially changed.

DEFINITIONS

Diuresis and Antidiuresis. Natriuresis and Antinatriuresis. The words "diuresis" and "antidiuresis" have frequently been used ambiguously to describe simply an increase or decrease in urine flow. One of the inferences reached in the following discussion is that, with certain qualifications,* the receptor : internuncial : effector systems involved in water conservation, on the one hand, and in sodium conservation, on the other, operate with complete independence of each other. Consequently *diuresis* and *antidiuresis* will be used here to designate an increase or decrease in the excretion of (osmotically free) water *per se*. An increase or decrease in sodium excretion will be designated as *natriuresis* and *antinatriuresis*.

With respect to the excretion of water, quantitative distinction is now made between water which is isosmotically obligated by urine solutes (osmolal clearance) and osmotically unobligated (solute-free) water which may either be added to or subtracted from this osmolal clearance to give, respectively, a "dilute" or "concentrated" urine [*127*]. This distinction has not been made in most of the literature reviewed here, however, and it has been generally necessary for me to evaluate diuresis and antidiuresis by changes in the urine concentration of one or more solutes (usually sodium or chloride), or sometimes by changes in urine

* The important qualifications are that (1) sodium and its salts are quantitatively the most important osmotic constituents in the extracellular fluid; (2) the excretion of a definite, small quantity of water is obligated by the excretion of urine solutes; and (3) the elaboration of osmotically free water during diuresis is subject to the delivery of at least an osmotically equivalent quantity of sodium (chloride) to the distal tubules.

flow alone. It is doubtful if this approximation has led to any serious errors of interpretation.

CENTRAL MECHANISM OF ANTIDIURESIS

See A, Figure 1

It is commonly accepted that changes in the excretion of osmotically free water are related to the antidiuretic hormone (ADH) secreted by the neurohypophysis in consequence of nervous or humoral excitation of the afferent pathways to this organ. Because of numerous central connections, neurohypophysial secretion can be excited by many diverse stimuli (pain, emotion, central vagal stimulation, cholinergic drugs, etc.), but the specific, physiologically effective stimulus involved in the maintenance of water balance is presumed to be the excitation of (hypothalamic?) osmoreceptors by an increase in the osmotic pressure of the blood [*110,139*]. It has been suggested that ADH acts by increasing the permeability of the distal tubule by the dilatation of pores, permitting osmotically free water to diffuse back into the blood [*119*]. No physiologic agent is known (apart from osmotic diuresis) which exerts an inhibitory effect on water reabsorption by the renal tubules. Thus the osmoreceptor:neurohypophysial:ADH system operates to maintain the osmotic pressure of the blood at a constant value by promoting the tubular reabsorption of water, and hence it will be designated as the "antidiuretic system."

VOLUME CHANGES RELATED TO ANTIDIURESIS

See B, Figure 1

Hemorrhage. It was as an integral part of Verney's classic studies of the humoral control of water excretion by the neurohypophysis that Rydin and Verney [*118*] first demonstrated, in the specific sense, that hemorrhage of moderate extent in the dog induces antidiuresis in consequence of the increased secretion of ADH. Adequate data on man are not available.*

Orthostasis. An antidiuretic situation in some ways paralleling hemorrhage, but one which has been more extensively studied, is presented by the circulatory insufficiency attending the passive, upright position, whether the subject is standing quietly or inclined 60° to 80° on a tilt-table. Here blood accumulates in the legs and the effective circulating blood volume is reduced; vasoconstriction increases the diastolic pressure and, until syncope supervenes, the systolic pressure tends to be maintained, reducing the pulse pressure; increased capillary pressure in the legs leads to excessive filtration of interstitial fluid, to reduction in the absolute plasma volume, and to increased hematocrit and increased plasma colloid osmotic pressure; and the venous pressure in the legs increases, although with no substantial increase in renal venous pressure.* Marked antidiuresis accompanies orthostatic circulatory insufficiency of even moderate degree, and Brun, Knudsen and Raaschou [*20,21*] have shown by a seemingly reliable test for ADH that concomitantly the secretion of this hormone is markedly increased. The pallor of syncope, which persists after recovery of the blood pressure and which occurs also in sympathectomized subjects, has been attributed to ADH [*39*].

Epstein et al. [*42*] have shown that orthostatic antidiuresis is not prevented by the infusion of iso-oncotic albumin solution (740 cc.)† and they conclude that it is not dependent on reduction of total plasma volume but on reduction of effective circulating blood and a redistribution of this blood. Bandaging the legs to prevent pooling of the blood is partially but not completely effective.‡ Pearce and Newman [*107*], Newman [*99*] and Kleeman et al. [*73*] have shown that alcohol,

* An antidiuretic response may be inferred from the data incompletely reported by Lombardo et al. [*90*] on venesection in man. Goodyer and Jaeger [*52*] showed that moderate hemorrhage in the anesthetized dog induces antidiuresis in the denervated as well as the innervated kidney, and concluded that the renal nerves are not involved in the response. However, antidiuresis was not observed by Brun, Knudsen and Raaschou [*21*] in four of five well hydrated subjects after withdrawal of 175 to 450 cc. of blood, but here hydration could have opposed an antidiuretic stimulus, a consideration not applicable to the other two studies. Lewis [*85*] has also shown that removal of 500 cc. of blood plus venous occlusion of the legs during near maximal water diuresis has no significant effect on the diuresis. Whatever antidiuretic action moderate hemorrhage may have, it is slight in comparison with the diuretic action of hydration.

* Increased renal venous pressure *per se* in the dog transiently decreases both sodium and water excretion [*13,58,68*] but it appears that this factor is involved to a negligible extent in orthostatic antidiuresis [*42*].

† Re-examination of their data, however, indicates that albumin at least ameliorated the antidiuresis and that its failure to be more effective may have been attributable to reduction in filtration rate.

‡ Antidiuresis occurs during exercise in the upright position [*70,99,107*] but not in the supine position [*50*]; Freeman et al. [*50*] suggest that the difference is referable to orthostasis itself.

which in adequate doses completely or nearly completely blocks the secretion of ADH, prevents orthostatic antidiuresis, confirming the neurohypophysial origin of the latter, while the antidiuresis in the vertical position is in large part offset by immersion in water up to the neck [*2*] and by hydration [*135*]. Conversely, orthostatic antidiuresis is potentiated by morphine [*85*], which releases ADH secretion.

The effect of posture led Harrison and his collaborators [*86,140*] to suspect that intracranial receptors may be involved, and to compare the effects of the sitting versus the supine* position on the excretion of dilute (0.14 per cent) saline. Urine flow and sodium excretion were generally greater in the supine position, but the relative rates of sodium and water excretion were highly variable, perhaps in part because the saline was administered orally. The investigators concluded that the effect of the sitting position could be partially but not entirely overcome by compression of the neck with a cuff inflated to 15 to 35 mm. Hg, but Netravisesh [*97*] and Barbour and his collaborators [*5*] have failed to confirm this result.

Venous Occlusion. Another approach to this problem is afforded by the demonstration by Wilkins and his collaborators [*151*] that antidiuresis is induced by obstructing the venous outflow from the thighs and one arm by the application of pressure cuffs inflated to subdiastolic pressure. Under these conditions over 700 cc. of blood and interstitial fluid may accumulate in the extremities [*37,84*]. Reduction of venous return reduces central venous and right atrial pressure [*141*], cardiac output [*49*] and right ventricular end-diastolic and pulmonary arterial pressure [*45*]. This antidiuretic response is not abolished by splanchnicectomy in hypertensive patients [*151*], but it is prevented by the prior administration of alcohol [*73*], facts which support the conclusion that it is a consequence of increased ADH secretion.

Farber et al. [*46*] established partial occlusion of the vena cava by a catheter carrying a balloon to be inflated after insertion. Decreased urine flow was observed after venous occlusion at any level (superior vena cava or inferior vena cava above or below the renal veins), although there were quantitative differences in intensity and speed of recovery depending on location. No distinction was drawn between antidiuresis and antinatriuresis, and no comment was made on the obligatory excretion of water at the low urine flows, but the data suggest that partial vena caval obstruction generally has an antidiuretic effect.

VOLUME CHANGES RELATED TO DIURESIS

See C, Figure 1

We turn now to procedures which induce diuresis (water excretion) without reduction in the osmotic pressure of the blood.

It is appropriate to note briefly a few papers frequently cited in this connection. Thompson [*136*] reported that the infusion of isotonic saline in dogs sometimes produced a substantial increase in the excretion of water without proportional salt, but his experiments were complicated by the use of morphine and ether-chloroform anesthesia and no data on filtration rate were available. Priestly [*112*] also reported a relative water diuresis in man, but here a slightly hypotonic, mixed salt solution was administered orally, a technic which may be criticized on several grounds.

Bazett and his collaborators [*7*] confirmed the then well recognized fact that a dilute urine may be excreted when a subject first assumes the recumbent position. They further showed that immersion up to the neck in a semi-reclining position in a covered bath at 36°c. had a further diuretic effect. Recumbency alone induced hemodilution, presumably in consequence of return of interstitial fluid to the blood; a warm bath induced hemoconcentration, presumably in consequence of peripheral dilatation and increased formation of interstitial fluid. Bazett et al. attributed the bath diuresis to pressure on the abdomen, increased venous pressure and redistribution of blood with splanchnic (and renal) dilatation, but these experiments are so complicated by temperature, posture, pressure and possibly cerebrocortical effects that at present they remain beyond interpretation.

Wilson and Harrison [*152*] obtained substantial diuresis in patients convalescing from infectious fever after the infusion of reconstituted

* Writers speak of the "recumbent" position, and the reviewer sometimes wonders if their patients had one, two or three pillows behind them. The angle of "recumbency" might make a significant difference in this problem, but the word supine has been used throughout the text.

The diurnal cycle in the excretion of water and electrolytes is a complicated one, but nocturnal antidiuresis (increased secretion of ADH) and antinatriuresis in normal subjects are clearly established [*87,88,124*].

plasma, but the endogenous creatinine clearance increased markedly in all but one patient and the composition of the urine was not reported. Metcalf [*93*] reported increased urine flow after infusion of serum and plasma into anesthetized dogs, but no data are available on the filtration rate. Similarly, Goodyer and Jaeger [*52*] found that reinfusion of blood in dogs after moderate hemorrhage increased the urine flow, but the data as reported (in per cent changes) permit only the conclusion that the infusions corrected the hemorrhagic oliguria.

Zuidema et al. [*156*] report that the infusion of plasma, normal saline and iso-oncotic albumin in dogs induces diuresis, but the magnitude of the diuresis was not large, the average maximal figure for these three procedures being 1.2, 1.3 and 2.3 cc./minute, respectively. The filtration rate was not followed and no information is given on the composition of the urine. The dogs had received morphine and were lightly anesthetized with chloralose; since the central effects of diuretic and antidiuretic stimuli are algebraically additive, medication may have reduced the magnitude of diuresis (even though morphine and chloralose were used in minimal doses) and thus worked against the success of the experiments.

Saline Solutions. The diuretic effects of saline became the subject of well considered investigation in 1951, when Blomhert, Molhuysen, Gerbrany, de Vries and Borst [*15*] of Amsterdam (see also Blomhert [*14*]), Strauss, Davis, Rosenbaum and Rossmeisl [*131*] of Boston, and Murphy and Stead [*95*] of Durham, simultaneously established that the infusion of isotonic saline into slightly hydropenic, supine subjects may induce a transient but substantial diuresis.* It was recognized that this diuresis is self-limited by progressive dehydration and elevation of the osmotic pressure of the blood, which would, of course, re-excite ADH secretion. Blomhert and his colleagues noted that infusion of a large quantity (amount unspecified) at a greater speed is followed by an increased excretion of salt as well as water. They also pointed out that diuresis induced at night by water *per os* is delayed and recovery is reduced. Drinking isotonic saline at night also leads to diuresis, but paradoxically the infusion of saline at night was without effect on urine production. These differences remain unresolved.

Strauss and his colleagues showed that isotonic saline induces diuresis only if the subjects are lying down, not if they are sitting up, an observation that led them to suggest that it is mediated through receptors sensitive to changes in the volume (or pressure) of the extracellular fluid and located in "the cephalad portion of the body."† However, diuresis is not promoted by tilting in the head-down position in man [*26,150*] or in dog [*100*].

Iso-oncotic Albumin Solutions. Of special interest is the demonstration by Welt and Orloff [*143*] that the infusion of about 2,000 cc. of iso-oncotic albumin solution (4 to 6 per cent in isotonic saline) induces a marked diuresis in nonhydrated subjects, a response blocked by pitressin.® The peak urine flow in one subject reached 15 cc./minute, and the average peak urine flow in six subjects was 8.9 cc./minute, or about 50 per cent of the anticipated maximal rate of diuresis in normal subjects when not overlaid on substantial osmotic diuresis. Welt and his collaborators [*109,143*] suggested that expansion of the plasma volume by the iso-oncotic albumin solution induced diuresis by inhibiting the secretion of ADH, and Welt and Orloff [*143*] (and a little later Strauss and his colleagues independently) referred definitively to "volume receptors," although they did not discuss their possible location.

Hyperoncotic Albumin Solutions. Orloff and Blake [*101*], working with mildly hydrated unanesthetized dogs, found that isotonic, hyperoncotic (25 per cent) albumin solution induced the substantial urine flow of 3 to 4 cc./minute per dog. This diuresis was blocked by pitressin and also by morphine (which releases ADH secretion), indicating a neurohypophysial origin.

However, Goodyer et al. [*53*] had earlier recorded that the infusion of such hyperoncotic albumin solutions in normal, well hydrated man induces some antidiuresis, an observation confirmed by Welt and Orloff [*143*] and by Petersdorf and Welt [*109*] in subjects undergoing near-maximal water diuresis as well as in subjects with diabetes insipidus. Because this antidiuretic action was greater when the albumin was given rapidly instead of slowly, and because it seemed to be ameliorated if saline (2.5 L.) had been given previously, Welt and Orloff [*143*] sug-

* This diuresis was only occasionally observed by Papper et al. [*105*].

† Strauss et al. [*131*] also suggest that the osmoreceptors of the neurohypophysial system may be sensitive to interstitial hydrostatic pressure as well as to osmotic pressure, but on the evidence this seems unlikely.

gested that it might be attributable to an increase in the plasma colloid osmotic pressure. As will be noted, however, hyperoncotic albumin solutions also induce antinatriuresis in man, and Petersdorf and Welt [*109*] later suggested that the increase in water reabsorption is passively related to increased sodium reabsorption. These investigators recognized that the rapid infusion of concentrated albumin solutions might induce ADH secretion by some other mechanism.

LOCATION OF VOLUME RECEPTORS INVOLVED IN ANTIDIURETIC SYSTEM

At this point we may note that among the suggested receptors or mechanisms relating water excretion to hemodynamic changes alone are: the kidneys themselves (Starling [*129*]); renal vasodilatation (Bazett et al. [*7*]); the cardiac output (Borst [*16*], Blomhert et al. [*15*], Wilkins et al. [*151*], Fitzhugh et al. [*49*]); renal venous pressure (Blake et al. [*13*], Hall et al. [*58*], Hwang [*68*]); the great veins (Farber et al. [*46*], Newman [*99*]); hemodilution without osmotic dilution (Blomhert et al. [*15*]); redistribution of circulating blood (Epstein et al. [*42*]) and specifically with altered arterial filling (Robinson [*114*], Epstein [*41*]); change in plasma or extracellular fluid volume (Orloff et al. [*101*], Welt et al. [*142,143*]); vascular volume (Cort [*29*]), or extracellular fluid volume generally (Leaf et al. [*83*]); both the plasma and extracellular fluid volume (Grossman [*57*]); the interstitial fluid in the legs (Pearce et al. [*106*], Newman [*99*]); the vascular or extracellular fluid volume in the head (Viar et al. [*140*], Lombardo et al. [*90*]); the extracellular fluid volume in the "cephalad portion of the body" (Strauss et al. [*131,132*]); and hydrostatic pressure effects on the osmoreceptors of the neurohypophysial system (Strauss et al. [*131*]). In short, despite consensus that an increase in volume of the blood, plasma or extracellular fluid can induce diuresis, and that a decrease can induce antidiuresis, there is no consensus as to where the receptors are located.

Negative Pressure Respiration. We turn now to a different approach which at least has the advantage of anatomic specificity. In 1947, Drury, Henry and Goodman [*35*], examining renal function in man during respiration against positive pressure (10 to 40 mm. Hg), a problem of practical interest to aviation medicine, observed that this procedure was accompanied by a marked reduction in urine flow and urea clearance. They considered antidiuresis to be a consequence of or a compensation for circulatory stress, since increased intrathoracic pressure impairs venous return and reduces cardiac output.*

Reversing this procedure in what were probably slightly dehydrated dogs, Gauer et al. [*51*] found that respiration against *continuous* negative pressure (−10 cm. water) induces, conversely, a slight increase in urine flow. (The filtration rate was not measured and no information is given on the composition of the urine.) Maximal diuresis in unanesthetized dogs, calculated as one-eighth of the filtration rate [*91,126*], would average about 0.5 cc./minute per kg., whereas negative pressure respiration increased the urine flow in the average from 0.03 to 0.066 cc./minute per kg., i.e. to only 12 per cent of this estimated diuretic level.†

The observations on man reported by Sieker et al. [*122*] are superior physiologically, and more impressive. In subjects who were mildly hydrated (priming of 300 cc. and ingestion of 50 to 100 cc. every thirty minutes of 0.14 per cent saline), continuous negative pressure respiration (−15 to −18 cm. water) transiently increased the urine flow (with dilution) from an average of 1.9 to 6.3 cc./minute, a level perhaps one-third of maximal diuresis, with only a slight increase in the endogenous creatinine clearance. The induction of diuresis in dog and in man by negative pressure respiration has been confirmed by Surtshin et al. [*134*], and in man by the measurement of the free-water clearance by Boylan and Antkowiak [*18*], while the last-named investigators have shown that the procedure is not accompanied by a decrease in plasma osmotic pressure.

Here, then, in isotonic saline administered in the supine position, iso-oncotic albumin in saline and negative pressure respiration, are three methods of inducing diuresis without an

* Positive pressure respiration in the dog [*74*] is accompanied by marked changes in renal hemodynamics and the procedure is mentioned here only because it supplied the point of departure for studies of the effects of negative pressure respiration on intrathoracic dynamics and diuresis.

† The degree of antidiuresis in the dogs studied by Gauer et al. [*51*] was unfortunately uncontrolled and undetermined. They were again premedicated with morphine and under light chloralose anesthesia, both of which circumstances may induce some antidiuretic activity, even though this antidiuretic activity may be inhibited by massive hydration. This criticism also applies to the experiments of Henry et al. [*61*].

apparent decrease in the osmotic pressure of the blood, as opposed to the fact that hemorrhage, orthostasis and venous occlusion induce antidiuresis without an apparent increase in osmotic pressure. We may now ask, do the various procedures which induce antidiuresis or diuresis have any hemodynamic consequences which, by activating or deactivating a common volume-sensitive system, might reverberate on the neurohypophysis?

Intrathoracic Blood Volume. The hemodynamic effects of continuous positive and negative pressure respiration have been extensively studied by Henry and his colleagues. As determined by plethysmographic methods, positive pressure respiration against 50 to 60 mm. Hg, the maximal pressure tolerable without syncope for thirty minutes at 18°c., displaces into the legs some 500 to 600 cc. of fluid (blood and interstitial fluid), a volume representing 10 per cent or better of the total blood volume. At 44°c. a larger volume, 800 cc. or more, may thus be displaced in a few minutes. Heat increases both the speed of displacement and the ultimate volume displaced because it dilates the arterioles of the skin and accelerates capillary transudation and filling of the venous reservoirs. Hence heat also speeds the onset of syncope [*59*].

The source of the blood displaced in orthostasis has been the subject of numerous investigations. Sjöstrand [*125*], reviewing the problem, concludes that 78 per cent is withdrawn from the thorax and the rest from the head, neck, arms, shoulders and hips, with only 2.5 per cent coming from the abdomen. Most of the thoracic contribution comes from the venous rather than the arterial side of the pulmonary circulation, and consequently the pulmonary veins and left atrium suffer the greatest reduction in pressure and volume. Henry [*60,62*] concludes that, despite the interposition of the right ventricle, the systemic veins, pulmonary veins and left atrium behave as one continuous elastic system and that moderate changes in blood volume are reflected by qualitatively parallel changes in left atrial pressure and volume. (Positive pressure respiration decreases cardiac output in anesthetized dogs, presumably by reducing right ventricular filling, but negative pressure respiration apparently does not increase cardiac output because right ventricular filling is limited by venous return [*122*].)

Left Atrial Stretch Receptors. The phenomenon of negative pressure diuresis is held by Henry et al. [*61*] to be related to left atrial filling because (1) distention of the pulmonary arterial tree (and right atrium) by multiple small emboli does not lead to diuresis; (2) a diuretic response is not obtained when the pulmonary veins are partially occluded close to the pericardium, distending these veins and the antecedent circulatory bed; (3) distention of the left atrium by a balloon, however, does induce transient diuresis despite the fact that this procedure can be expected to reduce cardiac output. These investigators conclude that stretch (or volume) receptors are located in the left atrium and possibly in the terminal part of the pulmonary veins located within the pericardium.*

The nature of afferent nerve fibers from these critical areas has also been examined by Henry and his colleagues [*60,61,63*] who conclude from their own evidence and from that of Paintal [*103*] that afferent impulses are carried centrally by the vagus. These impulses are believed to arise in stretch rather than pressure receptors because blood infusion, negative pressure respiration and balloon distention of the left atrium increase their frequency and the frequency is increased during atrial diastole rather than systole. Cooling of the vagus to 8°c. abolishes these impulses and also abolishes left atrial distention diuresis.

By way of a working hypothesis, we may tentatively accept the existence of stretch receptors in the left atrium and intrapericardial pulmonary veins which are excited by atrial distention during diastole (rather than during systole). (See D, Fig. 1.) It seems a necessary addition to the description to suppose that activation of the related afferent pathways exerts an inhibitory influence upon the neurohypophysial system, a supposition in no way novel because, as noted previously, it is well established that this system is subject to neural excitation and inhibition mediated by way of hypothalamic connections, even though the prepotent modality of excitation is through the osmoreceptors. The cyclical excitation of these atrial receptors at each diastole could, by algebraic summation with other factors, influence the level of activity of the neurohypophysial system and the secretion of ADH.

* Objections to the idea of stretch or volume receptors may be met by noting that many receptors (proprioceptors in muscles, tendons, baroreceptors in the arterial tree, cochlea, etc.) in the common view are activated by deformation or stretch, rather than by pressure itself. The receptors approaching most nearly true 'pressure' receptors are those of touch.

Carbon Dioxide Diuresis. One other diuretic phenomenon may be mentioned before closing this section. It has been known for many years that breathing gas mixtures containing 5 per cent or more of carbon dioxide induces an increased urine flow. Barbour et al. [*5*] have demonstrated in "recumbent" subjects that this represents a water diuresis which is not attributable to osmotic dilution of the blood—it may actually occur in the face of an increase in osmotic pressure; it is not related to an increase in the filtration rate, and it is inhibited by pitressin and not accompanied by an increase in sodium excretion. During prolonged breathing of carbon dioxide the diuretic effect reaches its peak in about fifty minutes and lasts for only some two hours. Barbour et al. [*5*] consider the possibility of intrathoracic receptors with scepticism, but I would be inclined to include carbon dioxide diuresis under the left atrial hypothesis if it could be assumed that it is not attributable to increased cerebral blood flow, and that carbon dioxide itself has no inhibitory effect on the central antidiuretic system. The latter assumption is not too safe in view of the ease with which this system can be excited or inhibited by emotional states, sensory stimuli, etc. [*110*]. However, Barbour et al. [*5*] report that inhalation of carbon dioxide did not produce diuresis in five of six tests on sitting subjects, an observation that rather argues against a chemical action and encourages further investigation.

Summary. As I interpret the foregoing evidence, the Henry-Gauer reflex from the left atrium is the only volume-sensitive system participating in diuresis-antidiuresis which has substantial evidence in its favor.

Setting aside hemorrhage (on which information is as yet inadequate in man), this hypothesis could qualitatively explain the antidiuresis induced by orthostasis, the sitting as compared with the supine posture and occlusion of the venous system by cuffing or intracaval obstruction, because these procedures decrease the venous return to the heart and filling of the right ventricle, decrease the stroke volume and pulmonary pulse pressure and (by inference, at least) decrease the diastolic distention of the left atrium. (This sequence would transpire even though the systemic arterial mean pressure were maintained by peripheral vasoconstriction, as does, in fact, happen early in moderate hemorrhage, orthostatic circulatory insufficiency and peripheral venous occlusion.)

Conversely, the left atrial receptors would be excited and diuresis would be favored by circumstances which increase the stroke volume and pulmonary pulse pressure and cause atrial diastolic distention, such as the infusion of isotonic saline, iso-oncotic (and hyperoncotic) albumin solutions (excluding the secondary effect of antinatriuresis), and (with due regard to the possible presence of ADH in the donor's plasma and excluding the correction of pre-existing oligemia) probably by the infusion of plasma or whole blood; and, of course, the diuresis of negative pressure respiration, the phenomenon which led Henry and Gauer to formulate their hypothesis. The hypothesis may also explain the often recorded fact that diuresis may be observed after the subject first assumes the supine position, when circulatory readjustments possibly enhance intrathoracic blood volume and left atrial filling. If one can argue that saline infused in the supine position expands the intrathoracic blood volume or increases left atrial filling for a longer period or to a greater extent than when infused in the sitting position,* the hypothesis will also explain the difference with respect to water excretion between the supine and sitting position without going further "cephalad" than the thorax.

The left atrial hypothesis, it may be noted, does not involve volume changes in the extracellular fluid. What is lacking to support it are studies in man confirming the hemodynamic effects of the procedures discussed here on left atrial (or pulmonary vein) diastolic pressure, or ideally (but perhaps unrealistically), on left atrial diastolic volume; and re-examination of the clinical circumstances enumerated under better controlled conditions, especially with reference to osmotic balance.

The tentative acceptance of left atrial receptors inhibiting neurohypophysial secretion does not, of course, exclude the possibility that other volume receptors, not yet identified, may serve a similar function.

EXAMINATION OF DIURETIC-ANTIDIURETIC PHENOMENA

Some technical difficulties in the study of this problem were not evident when the investiga-

* The infusion of saline (1,000 cc. at 77 to 146 cc./minute) into "recumbent" subjects increases pulmonary arterial and pulmonary capillary pressure [*35*] and it may be presumed that pulmonary venous and left atrial pressure are also increased.

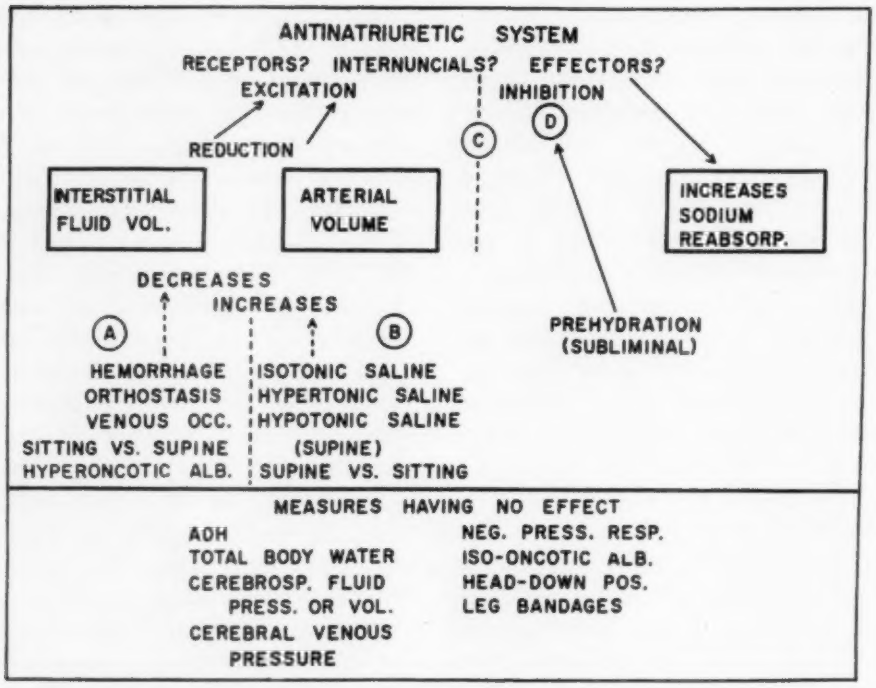

FIG. 2. Schema showing possible inter-relations between volume receptors and the antinatriuretic system, as the latter is conceived in the discussion. The encircled letters supply reference points in the text.

tions recorded were carried out. One consideration is that the immediate state of water balance of the subject can be defined and perhaps improved; obviously an antidiuretic effect cannot easily be established when ADH secretion is nearly maximal, nor can a diuretic effect be established when ADH secretion is minimal. *A priori*, one may conceive that the most appropriate steady state for such studies would be one of exact water balance, as indicated by an osmotic U/P ratio of 1.0. Man, (like the dog) when taking water *ad lib.*, generally operates in a moderate though not maximal antidiuretic state as indicated by an osmotic U/P ratio greater than 1.0. To achieve an osmotic U/P ratio of 1.0 (which indicates no net loss or gain of water in the body), a sufficient quantity of exogenous water must be administered steadily to counterbalance the simultaneous osmolar clearance [*127*]. Observations in this laboratory show that in sixteen hospitalized subjects subsisting on a *mixed* ward diet the postabsorptive osmolar clearance averages 2.29 cc./minute (range 1.38 to 3.00 cc./minute) per 1.73 square meter [*17*]. This figure will, of course, vary with salt and protein intake, and its prior estimation in any subject will remain largely a matter of guesswork. However, using the figure 2.3 cc./minute simply for discussion, to attain an osmotic U/P ratio of 1.0 requires that the subject receive a priming dose of water (perhaps 500 cc.) followed by the constant administration, orally or intravenously (perhaps best as 5 per cent glucose) of additional water at a rate of 2.3 cc./minute. (Here we ignore endogenous water liberation which will be roughly balanced by insensible water loss).

Second, it is no longer adequate to report (water) diuresis or antidiuresis simply in terms of changes in urine volume or the concentration of a single solute; the free-water clearance (C_{H_2O}) should be distinguished from the simultaneous osmolar clearance by appropriate measurements of the osmotic pressure of plasma and urine [*127*].

The use of anesthesia or morphine in animals should be avoided whenever possible, and in man due consideration should be given not only to psychogenic factors, posture, etc., but to the previous history of the subject with respect to hydration, as discussed later in this paper, and possibly to the intake of salt and protein.

ANTINATRIURESIS

See A, Figure 2

Where the prepotent stimulus to water conservation—increase in the osmotic concentration

of the plasma (and interstitial fluid)—has been clearly established, the equivalent stimulus to sodium conservation continues to be elusive. As noted earlier, it has long been thought that some aspect of the volume of the body fluids takes precedence over the plasma sodium concentration and other clinically measured terms, and it is with this volume element that this section deals.

We need not here be concerned with the neurohypophysis because the evidence preponderantly indicates that ADH is not directly concerned in sodium balance in man. The literature up to 1950 has been cited [*126*], but more recent studies have added new evidence to the conclusion that ADH has no direct action on sodium excretion (Sinclair-Smith et al. [*123*], White et al. [*147*], Chalmers et al. [*27*], Black et al. [*11*], Murphy et al. [*95*], Holland et al. [*67*], Ladd [*78*], Stanbury and Thompson [*128*], Nelson et al. [*96*], Weston et al. [*146*], Selkurt [*120*], Davis et al. [*33*]). An apparent exception to this negative opinion is afforded by the data of Ladd [*78*], which will be discussed later. Conversely, sodium retention induced by constriction of the inferior vena cava below the diaphragm is not dependent on the neurohypophysis or water intake [*80*].

Acute hydration may occasionally reduce sodium excretion slightly (Kattus et al. [*70*], Darragh et al. [*32*], Urbach et al. [*137*]); but Leaf et al. [*82*], Weston et al. [*146*] and Cheek et al. [*28*] have argued that the sustained hydremia and expansion of body fluid volume which ensue when pitressin is given in small doses over long periods lead to increased sodium excretion as an indirect homeostatic response. A possible explanation of this delayed natriuresis during hydration has been offered by Wrong [*154*] and will be discussed later.

Hemorrhage, Orthostasis and Venous Occlusion. Decreased sodium excretion (by exclusion of changes in filtration rate here taken to represent increased tubular reabsorption) is observed in hemorrhage [*52,90,98*], and in orthostasis [*42,54,70,107,148*]. Orthostatic antinatriuresis* is substantially reduced by bandaging the legs [*107*], but it is not blocked by alcohol [*107*] (which blocks moderate antidiuresis by neurohypophysial inhibition), by hydration [*135*] or by sympathectomy [*41*]; and increased reabsorption of sodium (chloride) occurs despite Na_2SO_4 diuresis [*43*]. The data of Epstein et al. [*42*] indicate that the infusion of 750 cc. of 4 per cent, or 300 cc. of 25 per cent albumin, did not wholly prevent antinatriuresis during orthostasis, whereas the infusion of 400 cc. of 6 per cent saline did prevent it despite some reduction in filtration rate. Both procedures were shown in some subjects to expand plasma volume.

Antinatriuresis is also induced by venous occlusion of the limbs by cuff [*49,151*] and by vena caval balloon [*46*] and possibly in the sitting as compared with the supine position [*86*].

Hyperoncotic Albumin Solutions. Goodyer et al. [*53*] found that concentrated albumin solutions, in amounts sufficient to expand the plasma volume by 20 per cent, markedly reduce sodium excretion in man, an observation confirmed by Welt and Orloff [*143*].† Petersdorf and Welt [*109*] showed that this antinatriuresis occurs during near-maximal diuresis in normal subjects and in patients with diabetes insipidus, ruling out the participation of the neurohypophysis. Orloff and Blake [*101*] did not consistently obtain an antinatriuretic effect with hyperoncotic albumin in the dog, but their failure to do so may perhaps be attributed to a counterbalancing increase in filtration rate in their experiments.

* The antinatriuretic effect of posture is exaggerated in patients with orthostatic hypotension [*3*].

Antinatriuresis occurs during mild exercise in the upright position (Kattus et al. [*70*]) but this may be in part referable to orthostasis since it does not occur during exercise of the legs in the supine position [*50*]. It may be noted that exercise in the supine position does not increase sodium excretion, even though it probably increases cardiac output and systemic pulse pressure.

Exercise in dogs does not alter the renal blood flow, filtration rate or sodium excretion, unlike man exercising in the upright position, suggesting either a species difference [*12,24*] or an effect in man related to orthostasis. It is not clear, however, that the severity of the exercise is physiologically equivalent.

† When given at night the albumin had little effect, but because of the diurnal cycle sodium excretion was very small at this time and further reduction could not be anticipated. The antinatriuretic effect was also demonstrated in a patient with Addison's disease (implying, with much other evidence now available, that tubular reabsorption of sodium remains under control in the absence of the adrenal glands). Welt and Orloff suggest that there might be intravascular "onco-receptors" which are activated by the colloid osmotic pressure of the blood.

Josephson and his colleagues [*69*] report that dextran in isotonic glucose is antinatriuretic in man, but the colloid pressure of the solutions used is not reported.

NATRIURESIS

See B, Figure 2

Whereas numerous circumstances induce unequivocal antinatriuresis, no physiologic circumstance is known which leads to equally unequivocal natriuresis except the administration of sodium chloride, and even here the magnitude of natriuresis, although highly variable, is frequently not very remarkable.* Doubtless in the long-range balance the sodium content of the body is of no less importance than its water content, but from moment to moment the sodium content is guarded more zealously. (Although, as we will see later, sodium can be excreted, relative to the filtered load, almost as copiously as water.) This parsimony should, perhaps, not be surprising. The regulation of the volume of the body fluids is a homeostatic problem not unique to the mammals; it has presumably been faced by the vertebrates throughout their fresh-water evolutionary history during which time water has generally been available in excess, sodium generally at a premium. Within limits, the organism can dispose of excessive sodium at leisure, whereas excessive loss leads quickly to critical depletion of the body fluids and to circulatory failure. Where "the mendicant position of the body fluids" once seemed to issue from the mere sluggishness or inefficiency with which excess sodium is excreted, rather than from any physiologic priority of sodium over water [*126*], we are now inclined to reverse the emphasis; over the short range sodium is more carefully conserved because, in the long range, it has been the most precious. This section can therefore begin appropriately with a negative accent.

Circumstances Not Significantly Affecting Sodium Excretion. As noted earlier, the present evidence argues against the conclusion that either ADH or total body water plays a direct (regulative) role in sodium balance.

It has frequently been observed that sodium excretion may be increased immediately after assuming the supine position, but such postural natriuresis is obviously transient and may be interpreted as merely reflecting the cessation of the antinatriuretic state activated by the antecedent orthostasis.

Reversing the sequence, Harrison and his colleagues [*86,90,92,140*] believed that cervical compression prevented the antinatriuresis induced by the sitting position or by moderate hemorrhage (2.5 cc./kg.), but control and experimental observations were made at intervals of several days; and in view of the rather small differences observed, and the wide variations known to occur from day to day, these observations fail to be conclusive.†

Sodium excretion is not affected by cervical compression in supine subjects, or by tilting in the head-down position in man [*5,26,41,92,97,140*], and the head-down position is without effect in the dog [*100*]. Nor does the effect of position in man seem to be attributable to dilatation of the venous system since bandaging the legs has no effect [*92*].

Fishman [*48*] has shown in the anesthetized dog that acute compression of the neck with a pressure cuff at 60 mm. Hg for thirty minutes, which increases jugular pressure by three-fold and cerebrospinal fluid pressure by two-fold, does not alter sodium excretion. Neck compression with simultaneous drainage of cerebrospinal fluid, to permit the intracranial veins to increase in both volume and pressure while decreasing the volume and pressure of the cerebrospinal fluid, was also without effect. Nor was sodium excretion modified by the injection of saline into the cisterna magna, increasing cerebrospinal fluid pressure to 500 mm. H_2O. (It may be noted that these procedures did not alter urine flow, filtration rate or PAH clearance.) Bull [*22*] has shown that decreasing cerebrospinal fluid pressure in man is also without effect.

It might seem that the antinatriuresis induced by hemorrhage, orthostasis and venous occlusion by pressure cuffs or vena caval balloon could be related to decreased filling of the intrathoracic circulation. Henry [*60*] holds to an unsettled opinion with respect to left atrial distention and natriuresis, but Sieker et al. [*122*], Surtshin et al. [*134*] and Boylan et al. [*18*] observed no consistent change in sodium excretion during negative pressure respiration in man, and Barbour et al.

* The sodium involved in ion exchange mechanisms—bicarbonate reabsorption and titratable acid excretion, K^+ excretion, etc.—is excluded from this argument because of independent physiologic regulation; we conceive that body fluid volume regulation centers on sodium chloride, and that sodium rather than chloride is specifically reabsorbed by the tubules.

† The reinfusion of blood after hemorrhage in dogs increases sodium excretion in both the denervated and innervated kidney [*52*], but one cannot judge from the reported data whether or not this represents more than the correction of the hemorrhage of oligemia. The infusion of plasma or blood in normal man has not been studied under well controlled conditions.

[*5*] observed no change during carbon dioxide inhalation, despite the positive effects of both procedures on the excretion of water.

One of the most surprisingly negative features of this problem is the failure of relatively large volumes (2,280 cc.) of iso-oncotic albumin (4 to 6 per cent) in saline to induce natriuresis, as reported by Welt and Orloff [*143*] and confirmed by Strauss et al. [*132*] a procedure which, as we have noted, produces a substantial diuresis. If changes in blood or plasma volume are related to sodium excretion this procedure would be expected to give a positive result, and it may be inferred that total circulating blood volume is not directly effective in determining sodium balance. Where changes in blood volume (hemorrhage) or in the distribution of blood (orthostasis, etc.) induce antinatriuresis, the immediate stimulus, it appears, must be sought in some derivative factor.

Saline Solutions. The most effective method of inducing natriuresis in normal subjects is the infusion of isotonic (or hypertonic) saline, the obvious effect of which is to expand the extracellular fluid. However, the natriuretic response in man is generally of slight or moderate magnitude, quite variable from person to person, and significantly modified by certain circumstances which require special consideration. The present discussion of saline natriuresis will therefore be restricted to a few papers which have a special bearing on the location of possible receptors.

Strauss et al. [*131*] had observed that sodium excretion is slightly greater during the infusion of saline in the supine position than in the sitting position.* These investigators went on to show that in well hydrated, supine subjects undergoing marked (water) diuresis, the infusion of 2 L. of hypotonic sodium chloride-bicarbonate solution increased sodium excretion even though the plasma sodium concentration was reduced. No natriuresis occurred in sitting subjects under the same conditions. The maximal rate of sodium excretion in these experiments was not large, but in view of (1) the absence of any increase in this figure in sitting subjects, (2) the failure of iso-oncotic albumin solutions to induce natriuresis as reported by Welt and Orloff [*143*] and confirmed by Strauss et al. [*131*] in this study, and (3) the fact that expansion of total body water by hydration does not have a natriuretic effect, Strauss and his collaborators attributed the natriuresis induced in the supine position by hypotonic saline to expansion of the extracellular fluid volume in the "cephalad portion of the body"—more "cephalad," perhaps, than in the case of the diuresis induced by isotonic saline (which we have tentatively referred to the left atrium).

LOCATION OF RECEPTORS

We are disinclined to accept the view that the receptors involved in sodium conservation are located in the extravascular fluid of the legs; however obvious the legs may be in man, they present a very recent problem in vertebrate evolution. It can also be doubted that extravascular receptors are restricted to the abdomen because the abdomen is too soft and patulous, and subject to too many changes in volume and pressure, in the Pisces, Amphibia and many of the Mammalia, including man.

The Venous System. The veins have long drawn attention in edematous states, but it seems unlikely that they are the locus of these receptors because they are readily distensible and the volume of blood in the venous reservoirs is highly variable and apparently not related to sodium retention. Circumstances which tend to collapse the peripheral veins, such as bandaging the legs of recumbent subjects [*92*] and tilting them into the head-down position [*26*], are without effect on sodium excretion. Hemorrhage

* Papper et al. [*105*] obtained a rather more consistent increase in sodium excretion after infusion of isotonic saline in supine subjects, and in the average excretion over a four-hour period observed no consistent difference between the responses to 340 mEq. of sodium chloride whether given as isotonic (0.9 per cent) or hypertonic (5 per cent) saline in the same subjects. They concluded from chloride space calculations that plasma sodium concentration and extracellular fluid volume are of similar importance in inducing natriuresis under the conditions of their experiments. It may be questioned whether the chloride space is valid for estimating extracellular fluid volume because the distribution of infused sodium chloride solutions is highly irregular, as judged by changes in the inulin space [*30*].

The infusion of 3 to 5 per cent glucose (25 cc./minute), a recognized method of inducing maximal diuresis, does not increase the excretion of sodium [*40*] in normal subjects, nor would one expect it to; the glucose is almost immediately removed by the tissues and such water as remains in the body at any moment is roughly distributed throughout the body water (about 60 to 70 per cent of body weight), with little effect on the volume of interstitial fluid (about 5 per cent of body weight). The maximal net effect is equivalent to the administration of water, although actually most of the water is quickly excreted in the urine.

of any substantial degree, which is probably accompanied by decreased venous filling; orthostasis, which distends at least the subcardial veins; opening an arteriovenous fistula, which locally increases venous pressure and venous filling [*44*], and venous congestion by pressure cuffs around the thighs are all effective in inducing antinatriuresis. Venous congestion of the legs is as effective in splanchnicectomized, hypertensive subjects as in normotensive or unoperated hypertensive subjects, and Wilkins et al. [*151*], referring to unpublished data, reject distention of the veins as the effective stimulus. In their study of the effects of vena caval obstruction by balloon, Farber et al. [*46*] concluded that if sodium retenton is related to vascular stretch, then the superior and inferior venae cavae react similarly and decreased sodium retention is not directly related to the increase in venous pressure peripheral to the obstruction.

Intrathoracic Vessels. The thorax may be excluded, possibly in its entirety, by the failure of negative pressure respiration [*18,122,134*] (and possibly carbon dioxide inhalation) [*5*] to increase sodium excretion.*

Intracranial Extravascular Location. If the receptors are extravascular, then it seems plausible, as Strauss et al. [*132*] first suggested, that they are above the thorax and, possibly as Strauss and his collaborators may have been thinking, in the *kephalios*, as the Greeks called the most anterior part of the body.

In this view, one would suppose that the receptors are related to some sharply delimited "pool" of intracranial interstitial fluid, so constituted that reduction in volume would lead to excitation of related receptors by deformation. If the simplicity of this interpretation is to be preserved, however, it must be supposed that this pool of interstitial fluid is subject to the Starling principle: i.e. we must conceive it to be formed by filtration across a local capillary plexus, and hence subject to the opposing forces of hydrostatic pressure and colloid osmotic pressure. Moreover, the capillary pressure itself must be subject to changes in antecedent arteriolar pressure, and hence in local arteriolar tone.

The last point raises an immediate difficulty for the intracranial interstitial hypothesis because of the seemingly unavoidable interposition of a variable arteriolar resistance proximal to the local capillary plexus; this has the consequence of raising the as yet unanswerable question whether or not the local resistance may change, with consequent changes in capillary pressure, in a manner parallel with, or independently of, changes in systemic arteriolar resistance.† Thus the effects of hemorrhage, orthostasis, venous occlusion and even the sitting versus supine posture—all of which elicit some vasomotor changes—cannot, under this hypothesis, be interpreted directly in terms of systemic hemodynamics and transcapillary fluid exchange.

Apart from this difficulty, intracranial interstitial fluid volume receptors could explain (1) why natriuresis is induced by hypotonic, isotonic, and hypertonic saline; such solutions all expand the interstitial fluid generally; (2) why hyperoncotic albumin solutions induce antinatriuresis; such solutions expand the plasma volume at the expense of the interstitial fluid and reduce the volume of the latter; (3) why large volumes of iso-oncotic albumin solutions do not induce natriuresis; such solutions, if truly iso-oncotic, would have no effect on interstitial fluid volume so long as they do not change the capillary hydrostatic pressure; and (4) the facts that spontaneous natriuresis tends to be greater, and that saline solutions tend to be more effective, in the supine than in the sitting position; nearly all investigators accept that a passive change in posture significantly affects the distribution of fluid between the vascular and the extravascular compartments, and it seems fair to accept that a smaller fraction of administered saline would accumulate in the intracranial fluid in the sitting position than in the supine position. (Here, however, one cannot exclude the intervention of vasomotor changes.) The hypothesis is at least compatible with the observation that bandaging the legs and tilting the subject in the head-down position are without effect.

Against the intracranial interstitial fluid hypothesis is (1) the failure of Epstein [*41*] to obtain any change in sodium excretion in conscious dogs when hyperoncotic albumin solution is infused into the carotid artery. (Examination of the protocol reveals, however, that the dogs were

* Voluntary hyperventilation increases sodium excretion but this may be referable entirely to respiratory alkalosis and increased bicarbonate excretion.

† Scarcely less important than the mean arteriolar (and capillary) pressure is the pulse pressure, which profoundly affects lymphatic drainage [*106,155*]. No information is available to the writer on the effects of pulse pressure on capillary filtration.

receiving 5 cc./minute of 0.9 per cent saline intravenously, equivalent to a load of 64.8 gm. of sodium chloride per day; this infusion had been maintained for some thirty minutes before the albumin was injected, and the control rate of sodium excretion was above 300 μEq./minute (25 gm./day); it is possible that increased filtration rate or other factors disposing towards natriuresis may have swamped an antinatriuretic stimulus of lesser intensity. This experiment is, however, critical, and unless it is negated by further studies without saline loading or otherwise explained, the hypothesis would be untenable without such modifications as would mean almost complete redefinition.)

Also against the hypothesis is (2) the presumed isolation of the receptor system from intracranial pressure. It is conceivable that a local pool of interstitial fluid might not be influenced by moderate changes in cerebral venous pressure; the interposition of a venular resistance beyond the capillary plexus (as in the venous tree of the kidney and other organs) [*75*] might maintain local venous pressure substantially higher than, and relatively independent of, the pressure in the jugular veins; hence the failure of cervical compression and of the head-down position in man to modify sodium excretion cannot be weighed too heavily. However, it is very difficult to explain the negative results in Fishman's [*48*] experiments in which, in the anesthetized dog, cervical venous pressure was increased by threefold (to or above 60 mm. Hg), and cerebrospinal fluid pressure by two-fold.

Cerebrospinal fluid is, of course, not interstitial fluid but a secretion isolated chemically (except for water) [*117*] from the latter (and from the plasma) by ependymal and neuroglial cytoplasm. But this chemical isolation affords no isolation against changes in intracranial venous (or capillary) pressure because the brain substance, grossly and microscopically, is extremely soft and deformable.

Consider, for argument, a deformable bag, impermeable except to water, filled with "interstitial fluid," the bag and its contents floating freely in cerebrospinal fluid; so long as the bag remains a completely closed system the application of hydrostatic pressure to the surrounding fluid would not deform it beyond the limits of the compressibility of water. But let the bag be penetrated by a plasma-filled capillary which is impermeable only to protein, converting it into a "Starling osmometer," and let the capillary contents be free to move along the capillary lumen; then changes in hydrostatic pressure in the surrounding fluid, transmitted by the deformable bag to its contents, will lead to transcapillary movement of the interstitial fluid and to changes in the bag's volume and hence to its deformation. So long as the "intracranial interstitial fluid" pool is contained within a deformable membrane, it seems impossible to escape the conclusion that "external" (cerebrospinal) hydrostatic pressure is equivalent to "internal" (interstitial) hydrostatic pressure in relation to transcapillary fluid movement and volume changes.

The argument applies with equal force to interstitial fluid throughout the body, and it may be that the interstitial (extravascular) hypothesis can be saved only by introducing a dynamic element or other novel feature.

Intra-arterial Location. An intra-arterial location for receptors mediating sodium conservation was implicit in the writings of Peters, Borst and others, but it was perhaps first explicitly stated by Epstein, Post and McDowell, [*44*] who related changes in sodium excretion to "the degree of filling of some portion of the arterial tree." It is no serious disadvantage to this hypothesis that the location of the receptors is not indicated by any available evidence, even though it seems improbable that receptors specific to this function are diffusely distributed throughout the arterial tree. An interesting alternative in this matter has been suggested by Robinson [*114*] who points out that changes in posture, etc. require immediate readjustments in vasomotor tone and that there may be afferents from blood vessels all over the body, signalling continuously the amount and distribution of peripheral vasoconstriction (or vascular filling) back to the vasomotor center. Such afferent impulses could conceivably converge also on central mechanisms controlling sodium conservation.

This hypothesis could explain (1) the antinatriuresis of hemorrhage, orthostasis, venous occlusion and the upright versus the supine position without invoking local vasomotor changes; these circumstances are all characterized by some decrease in cardiac output and pulse pressure, and hence probably by decreased arterial distention. (It must be noted, however, that "arterial distention" is difficult to assess and cannot be judged from mean arterial pressure, pulse pressure or cardiac output alone.)

The intra-arterial hypothesis is also compatible with the failure of leg bandages or tilting the subject in the head-down position to influence sodium excretion.

Against the intra-arterial hypothesis is the fact that (1) large volumes (2,280 cc.) of iso-oncotic albumin given intravenously do not increase sodium excretion. This negative result requires that the fluid be quickly sequestered by vasodilatation in some segment of the vascular tree so that it does not increase the filling of the sensitive part of the arterial reservoir; (2) nor does this hypothesis explain the antinatriuresis induced by the infusion of hyperoncotic albumin in man. Such solutions quickly expand the plasma volume at the expense of the interstitial fluid, and the increment in plasma volume should have no effect, one thinks, other than that of a similar volume of iso-oncotic solution; (3) lastly, the natriuretic effect of isotonic and hypotonic saline are not readily explained by expansion of any part of the arterial tree because these fluids are rapidly distributed between the blood and the interstitial fluid, and insofar as they remain in the blood, probably expand the venous system more than the arterial system. Perhaps it may also be counted against the intra-arterial hypothesis that (4) thoracolumbar sympathectomy, traumatic or pathologic transection of the cervical spinal cord in the absence of shock, and thoracic vagotomy (lower third, exclusive of a few concealed fibers), are not separately accompanied by disturbances in sodium balance (so far as the writer can learn from his surgical advisors), which taken collectively would leave intra-arterial receptors without an afferent neural path unless they are located in the heart, aortic arch or cervical-cranial arteries.

Robinson's [*114*] alternative suggestion, that the efferent (vasomotor) paths to the blood vessels might branch and convey to some subcortical center "for information" a copy of the orders going out as constrictor impulses to the blood vessels "for action" is worthy of serious consideration as a subsidiary mechanism, but has many difficulties in its way as a primary and primitive device for the homeostatic control of sodium conservation.

Summary. Although much of the evidence cited is to some degree ambiguous, especially in respect to possible changes in filtration rate under circumstances promoting antinatriuresis and natriuresis, this evidence, we believe, favors the thesis that volume receptors are, indeed, involved in sodium conservation. But where these receptors are located remains a moot question. Only two locations are supported by any substantial arguments; the intracranial interstitial fluid and the arterial tree (as a whole or in some unspecified part). The intracranial interstitial hypothesis has two counts against it, the intra-arterial hypothesis, four, but since it is better to weigh the evidence than to count it, we must admit to our inability to decide between (1) the intracranial interestitial hypothesis, (2) the intra-arterial hypothesis, (3) whether or not there are several qualitatively different systems of receptors variously situated throughout the body (which we can call the multiple nature hypothesis), or (4) whether or not there are any such receptors at all (which we can call the Cheshire Cat [*25*] hypothesis).

EVIDENCE FOR THE EXISTENCE OF A CENTRAL, INTEGRATED ANTINATRIURETIC SYSTEM

Except under (4), questions can still be raised, however, concerning the integration of sodium conservation with renal function in particular, and water balance in general.

To this end, we will outline a tentative syllogism, one rather more detailed than has been hitherto proposed, within which to interpret certain phenomena yet to be discussed. Apart from immediate convenience, perhaps the only service of the syllogism will be to stimulate further experimentation and to give investigators a definitive target to annihilate *seriatim* if not immediately *in toto*. (Nor can all the presently known facts be immediately reconciled with any syllogism.)

In the following discussion we will speak of the "antinatriuretic system" because, so far as we know, all changes in sodium (chloride) excretion result from promotion of tubular reabsorption (an antinatriuretic process); no factor is known (other than organic mercurials, etc.) which inhibits tubular reabsorption or promotes active tubular excretion.

The regulation of the volume of the body fluids and hence of sodium conservation, we have noted, presents a problem which has presumably been faced by the vertebrates throughout their evolutionary history. Apart from other evidence, this circumstance would seem to justify the search for an antinatriuretic system which, by supplementing the antidiuretic system,

would subserve the ends of body-fluid volume regulation.

In keeping with seemingly adequate physiologic precedents, we suppose that this antinatriuretic system contains the three formally identifiable components of the reflexes of the neuraxis: (1) receptors (location unspecified, but analogous to the osmoreceptors of the antidiuretic system); (2) internuncials (intercalated paths which may be neural, humoral or both, and analogous to the supraoptico- and paraventriculo-neurohypophysial tracts); (3) effectors (one or more humoral agents, analogous to the antidiuretic hormone, which promote sodium reabsorption by the renal tubules).*

Regardless of the nature and location of (1) and (2), it is to be anticipated that (2) in the course of vertebrate evolution would have been incorporated in the central nervous system and integrated with other neural pathways, in a manner analogous to the osmoreceptor-neurohypophysial system. (See C, Fig. 2.) The experiments to be discussed supply, we believe, suggestive evidence, if not for central representation, at least for integration somewhere.

Returning to the fate of intravenously administered saline, the literature on this subject is so large that only certain pertinent studies can be cited.

Excretion of Saline in the Dog. Green and Faragh [*55*] showed that after the infusion in dogs of sodium chloride solutions, ranging in concentration from 5.15 down to 0.145 M., sodium excretion was markedly increased, the excretion fraction† in one instance reaching the phenomenal figure of 41.8 per cent, and frequently ranging between 20 to 30 per cent. Green and Faragh suggested that sodium excretion is conditioned, not in the interest of sodium conservation, but rather of osmotic homeostasis. In view of other evidence, however, it seems preferable to adhere to the view that osmotic homeostasis is maintained through the antidiuretic system. Green and Faragh believed that sodium excretion is not related consistently to the filtration rate, but later studies have shown that the filtration rate is a very important factor.

Wesson and his colleagues [*145*] had at this time been examining the effects in the dog of the sustained expansion of the extracellular fluid by a constant volume, maintained for periods up to eight hours and with minimal change in plasma electrolyte composition by the reinfusion of urine. After such expansion, both filtration rate and tubular reabsorption of sodium show a bimodal phasic response, indicating profound but slow readjustments in both functions. At the time when the filtration rate reached its maximal value, 15 per cent of the filtered sodium was excreted; but subsequently, at the same filtration rate, this fraction decreased, in consequence of increased tubular reabsorption, to some 7 or 8 per cent. This appears to be the first quantitative demonstration that under conditions in which no identifiable factor other than extracellular fluid volume (and plasma protein concentration) is altered, and in which the filtration rate is constant, tubular reabsorption can undergo marked alteration. But these experiments, as well as the experiments of others, show that an increase in filtration rate alone, with presumably minimal change in tubular activity, can increase sodium excretion markedly. It is certainly in part because of these readjustments in the filtration rate that the dog, when infused with 5 per cent saline, can increase the excretion fraction to 30 per cent or better [*121*]. So effective is the excretory adjustment that this animal can tolerate massive quantities of salt in the diet (4 gm./kg. per day, equivalent in man to 280 gm. per day) for periods up to six days without gain in weight or change in plasma sodium concentration. Under these conditions the filtration rate may increase by 100 per cent after salt ingestion, and over a twenty-four hour period more than 10 per cent of the filtered sodium may be excreted [*79*]. If man behaved like the dog, he could maintain himself in salt balance on substantially more than 100 gm. per day. Obviously man does not behave like a dog.

Saline-induced Natriuresis In "Normal" Subjects. When the reader studied physiology he possibly participated in a laboratory experiment which is still popular with instructors in that discipline,

* Despite continuing debate, we set aside as without adequate foundation the belief that the renal nerves play any role in the control of sodium excretion beyond those effects which may issue from changes in vasomotor activity [*102,120*].

† The per cent of filtered sodium excreted in the urine. Ignoring the Donnan factor, *k*, this fraction is identical with the clearance ratio $C_{Na}/C_F \times 100$, and is generally calculated from the filtered load of sodium; but as Wesson and Anslow [*144*] have pointed out, the reabsorption of bicarbonate, phosphate and some organic anions and the potassium ion exchange mechanism entail the obligatory reabsorption of equivalent sodium, and the specific conservation of sodium is better revealed by the excretion fraction of chloride.

if not with the students. The First Year Class is divided into two groups, the sheep and the goats; the sheep drink a liter of tap-water, the goats a liter of 0.9 per cent saline; both groups are instructed to collect urine at intervals until the 'diuresis' is over. The tap-water group, of course, gets a rapid diuretic response which is over in two to three hours and then they write up their notes and go home. The saline group wait and wait for something to happen and may still be waiting at 5:00 o'clock and wondering whether they have subclinical renal disease or are in a latent state of cardiac failure. There is one pretty certain fact, and that is that they never find out what became of the saline. The half-life of a liter of isotonic saline in man is generally a good many hours, even after intravenous infusion.

The short-range aspects of this problem were examined by Crawford and Ludemann [*31*] who confirmed the universal experience of the First Year Class. When "normal" subjects (editors wisely recommend that quotation marks be used or the word replaced by "subjects without evidence of cardiovascular-renal disease," etc.) receive 1 to 3 L. of isotonic saline intravenously at a rapid rate (13 to 56 cc./minute), sodium excretion during the next three and a half hours (when water diuresis would be largely finished) increases only moderately. The three- to four-hour excretion of equivalent quantities of sodium chloride in 5 per cent saline is scarcely greater, as shown by Papper et al. [*105*], but Baldwin, Biggs and Hulet [*4*] have recently found that 2.5 per cent saline when infused for relatively long periods can induce a remarkable natriuresis at the peak of the response. In normotensive subjects infused for only one hour, the excretion fraction during the last twenty minutes of infusion averages 2.3 per cent, but if the infusion is continued for two to three hours, this figure for the last twenty minutes reaches 9.7 per cent.* (See Fig. 3.) It is clear, however, that as compared with the dog, man excretes saline very sluggishly, and certainly one important reason for this is that in the face of expansion of body fluids the filtration rate does not increase as it does in the dog, a species difference for which no explanation is available.

Saline-induced Diuresis in Prehydrated Subjects. Examination of possible variables involved in the response to saline led Ladd [*76*] to the study of the effects of prehydration. In control subjects who had received no fluid during the preceding thirteen to seventeen hours, Ladd found, as others had, that after the infusion of 3 L. of saline (at 45 to 65 cc./minute), the urine flow typically increased only moderately (peak values averaged about 3.0 cc./minute with a maximal figure of 3.5 cc./minute). The urine remained slightly hypertonic (osmotic U/P ratio above 1.0), indicating the persistence of mild antidiuresis.

If, however, the subject is massively *prehydrated* by drinking as rapidly as possible (in fifteen to sixty minutes) 2 L. of tap water at a period eight to thirteen hours before the saline infusion, then this infusion generally induced a remarkable and apparently *maximal water diuresis.* The urine flow reached a maximal value fifty-five to sixty-five minutes after the start of the infusion, this maximum being maintained for nine to twelve minutes. The peak urine flow ranged from 9.8 to 36 cc./minute and averaged 19.3 cc./minute, as compared with 3 cc./minute in the non-prehydrated subjects. The maximal free-water clearance at the peak value is identical with that observed during the diuresis induced by 1.5 to 2.5 L. of tap water taken orally in the same subjects [*78*]. This diuresis is prevented by pitressin, indicating that the renal tubules have not lost their sensitivity to ADH; and it is reduced by the infusion of hypertonic (1.2 to 1.5 per cent) saline, implying that the osmoreceptor-neurohypophysial system is not incapacitated. Nevertheless, the diuresis occurs in the face of a normal or even elevated plasma osmotic pressure.

That the induction of diuresis in prehydrated subjects by isotonic saline is not attributable to the persistence of excess water in the body after prehydration is indicated by the fact that if the interval between prehydration and saline infusion is less than eight hours, the diuresis is greatly reduced in magnitude [*76*].† That the change in the responsiveness of the osmoreceptor-

* The longer infusion involves 231 to 318 mEq. of sodium, as compared with the 340 mEq. given by Papper et al. [*105*] who report only the average excretion over a four-hour period. It may also be noted that in the three subjects examined by Birchard, Rosenbaum and Strauss [*9*] the estimated peak excretion fraction after 2 per cent saline (1,000 cc. in sixty minutes) reached the unusual figures of 5 to 5.8 per cent.

† In non-prehydrated subjects, the maximal diuretic response to 1.5 to 2.5 L. of ingested water is reached in 100 to 120 minutes [*78*], and presumably in eight to thirteen hours nearly all the water involved in prehydration would be excreted.

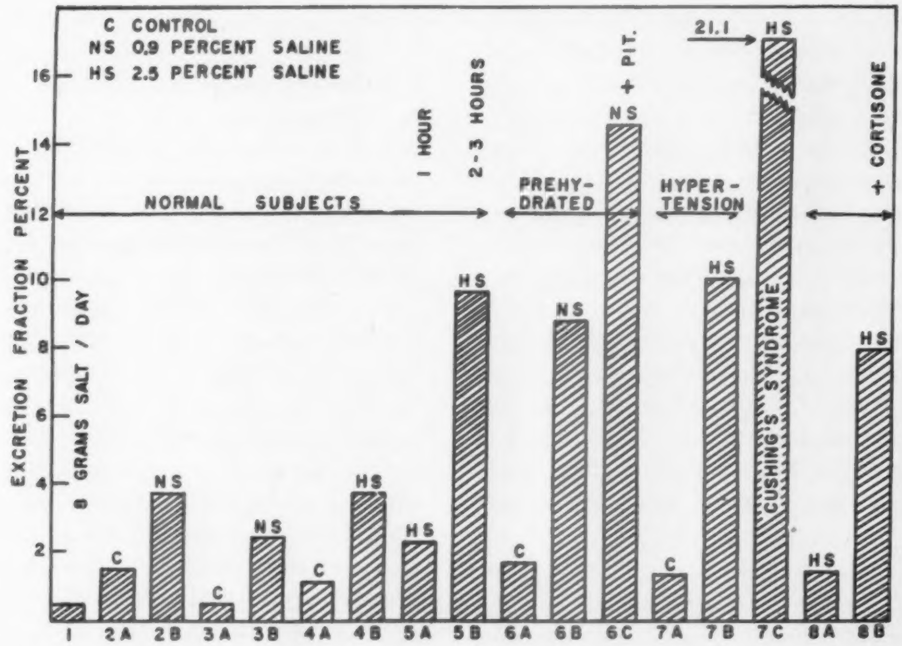

FIG. 3. Sodium (or chloride) excretion fraction (EF) in man (4, 7 and 8 refer to chloride excretion fraction). 1, Estimated EF (0.53 per cent) on 8 gm. salt/day. (Filtered load taken as 18 mEq./minute, UV as 0.095 mEq./minute.) 2A, Average EF in single periods for each of three patients, postabsorptive [*131*]. 2B, average max. EF in six patients after 3 L. of 0.9 per cent saline at 25 cc./minute [*131*]. 3A, Average EF for ten unhydrated subjects, postabsorptive [*77*]. 3B, Average maximum EF for nine unhydrated subjects after 3 L. of 0.9 per cent saline at 45 to 65 cc./minute [*77*]. 4A, Average EF in three periods in each of seven subjects [*8*]. 4B, Average maximum EF in same seven subjects after 2.5 per cent saline (11.25 cc./kg. in forty-five minutes supplemented by 20 cc./kg. water orally) [*8*]. 5A, Average EF in thirteen subjects during last twenty minute period of one hour infusion of 2.5 per cent saline (12 to 13 cc./minute) [*4*]. 5B, Average EF in ten subjects during last twenty minute period of two to three hour infusion of 2.5 per cent saline (12 to 13 cc./minute) [*4*]. 6A, Average maximum EF in seventeen subjects prehydrated (2 L. tap water orally) eight to thirteen hours previously, no infusion [*77*]. 6B, Average maximum EF in eighteen subjects prehydrated as in 6A and infused with 3 L. of 0.9 per cent saline (45 to 65 cc./minute) [*77*]. For other data on prehydration plus saline see Table I [*78*]. 6C, Average maximum EF in twelve subjects prehydrated and infused with 3 L. of 0.9 per cent saline as in 6A and with pitressin® 0.3 to 1.0 mμ/kg. per hour [*78*]. 7A, Average EF in eight hypertensive subjects receiving no infusion [*8*]. 7B, Average maximum EF in eight hypertensive subjects after infusion as in 4B [*8*]. 7C, Single period maximum EF in a patient with Cushing's syndrome after infusion as in 4B [*8*]. 8A, Single period maximum EF value in a normal subject, E. C., after infusion as in 4B [*8*]. 8B, Single period maximum EF in E. C. pretreated with cortisone (see text) and infused as in B4 [*8*].

neurohypophysial system is transitory is indicated by the fact that the diuretic response is not obtained if prehydration and saline infusion are separated by an interval greater than thirteen hours.

Saline-induced Natriuresis in Prehydrated Subjects. Ladd [77] found that prehydration had similar consequences with respect to sodium excretion after saline infusion. The excretion fraction in non-prehydrated subjects before infusion averaged only 0.46 per cent; after saline (3 L.) this figure reached an average peak value of 2.5 per cent, a substantial although not dramatic increase.* (See Fig. 3.) In subjects who had been prehydrated, however, the excretion fraction before infusion averaged 1.7 per cent—i.e. prehydration alone seems to leave a trace effect predisposing the natriuresis. But when prehydrated subjects are infused with saline (3 L.), the peak excretion fraction averaged 8.8 per cent, with one value above 12 per cent. (These data are calculated from the filtered load of sodium; if calculated from the filtered load of chloride in order to exclude bicarbonate, etc., the excretion fraction would be increased by some 25 per cent of the reported values.) This increased sodium excretion is attributable only in small part to increased filtration; most of the increase represents decreased tubular reabsorption. Assuming a filtration rate of 12.7 mEq. of sodium chloride per minute (102 mEq./L. × 125 cc./minute), an excretion fraction of 8.8 per cent would represent the excretion of 1,610

* Similar excretion fractions after isotonic saline are reported by Wiggins et al. [*149*], Papper et al. [*105*] and others.

mEq. (94 gm.) of sodium chloride per day, enough to remove all the sodium chloride in the body (about 2,000 mEq.) in thirty hours.

The natriuresis induced by saline in prehydrated subjects is wholly dissociable from the simultaneous diuresis; when the latter is blocked by the administration of pitressin, natriuresis is, in fact, increased; the peak excretion fraction of sodium in prehydrated subjects receiving saline and pitressin simultaneously averaged 14.7 per cent, as compared with 8.8 per cent without pitressin [*78*].* This peak excretion represents 158 gm. of sodium chloride per day and would drain all the sodium chloride out of the body in fifteen hours. Fortunately, both the natriuretic and diuretic phenomena are self-limited.

INHIBITION IN THE ANTIDIURETIC SYSTEM

These phenomena, and others to be cited, at first glance seem inexplicably complex, but they may be reduced, we believe, to a simple pattern if we suppose that various afferent impulses on reaching the hypothalamic antidiuretic system (osmoreceptors-neurohypophysial tracts-ADH secretion) may exert either an excitatory or inhibitory effect, and that effects of the same sign may be arithmetically additive, effects of opposite sign, algebraically additive. (See E, Fig. 1.)

It is commonly accepted that "increasing" the osmotic pressure of the body fluids "excites" the osmoreceptors of the neurohypophysial system; in these terms, hydration of the body decreases ADH secretion simply by decreasing or removing entirely the primary excitatory stimulus. Alcohol in moderate doses, however, produces diuresis at a constant plasma osmotic pressure [*73,116,133,138*],† and it will prevent the antidiuresis induced by moderate amounts of hypertonic saline if the two are administered simultaneously [*73*], presumably because it exerts an inhibitory effect at some point in the antidiuretic system. (Numerous other examples involving pain, excitement, anesthesia, conditioned reflexes, etc. involving neural excitation or inhibition of the antidiuretic system might be mentioned.)

It has previously been argued that afferent pathways from the left atrium can also induce diuresis at a normal (antidiuretic) plasma osmotic pressure; this phenomenon again implies inhibition at some point in the antidiuretic system by vagal afferent impulses, offsetting the normal activity of the osmoreceptors. Hence it may be presumed that the activity of this system at any moment reflects a balance between inhibitory and excitatory stimuli.

One possible interpretation of the (water) diuresis induced in prehydrated subjects by isotonic saline is that after the prehydrating dose of water is excreted and the osmotic pressure is restored to normal values, there remains a trace effect within the antidiuretic system which takes the form of a latent or subliminal inhibition. Although ADH secretion is resumed after the water has been excreted, this subliminal inhibition continues to increase in intensity, to reach a maximum some eight hours after prehydration (four or five hours after most of the prehydrating water has been excreted), at which time a second inhibitory stimulus, initiated by the infusion of 3 L. of isotonic saline, acts summatively to effect *complete* inhibition and consequently to produce *maximal* diuresis.

This interpretation involves two novel features: long persistence of inhibition and potentiation with the passage of time. With respect to the first, it may be noted that excitation and inhibition in the neuromuscular system are generally of short duration (milliseconds); however, post-tetanic potentiation in a monosynaptic spinal reflex may last for some minutes, the persistence of potentiation increasing with the intensity and duration of afferent stimulation [*89*]. Again, "use" in a spinal reflex may lead to increased synaptic function, disuse to prolonged decreased synaptic function [*38*]. Of greater interest to the present problem are the observations of Hernandez-Peon and his collaborators that photically evoked activity in the lateral geniculate body [*64*], on the one hand, and acoustically evoked activity in the cochlear nucleus [*65*], on the other, can be inhibited (habituation) for as long as twenty-four and fifteen hours, respectively, by repetitive photic or acoustic stimuli. In both instances the persistent inhibitory effect appears to be related to

* In an earlier footnote we mentioned this paper as a notable instance in which pitressin appears to have had a natriuretic effect. An alternative explanation, however, is that by preventing the excretion of water, pitressin leads to the further expansion of body fluid and increases it to a degree beyond that afforded by saline expansion alone.

† Rubini et al. [*116*] have shown that alcohol also tends to decrease sodium excretion, but this effect is neither very marked nor consistent.

long collateral pathways in the reticular formation of the brain stem.

Progressive intensification of the posited "inhibitory effect" in the antidiuretic system has no analogy, so far as I know, in sub-cortical neurophysiology. Progressive potentiation of inhibition after cessation of an inhibitory stimulus is a well recognized phenomenon in the conditioned reflex, but here cortical pathways are presumably involved, and no cortical participation is posited in the present hypothesis. The difficulty presented by what we have called "progressive potentiation of subliminal inhibition" may be semantic rather than real, because in both the antidiuretic and antinatriuretic systems (*vide infra*) as here conceived, we are probably dealing with receptor-internuncial-effector systems much more complex than monosynaptic reflexes, and possibly involving neural or neurohumoral cumulative effects arising external to these systems.

CENTRAL INHIBITION IN THE "ANTINATRIURETIC SYSTEM"

Paralleling the interpretation proposed for the antidiuretic system, we suppose that expansion of the body fluids (or increased intra-arterial filling) leads primarily either to cessation of activity in (or inhibition of)* the antinatriuretic system, and thus to increased sodium excretion. (See C, Fig. 2.) That the natriuresis so induced is rarely maximal is shown by the facts that 3 L. of isotonic saline increase the sodium excretion fraction in the average to only 2.5 per cent [77], whereas a two- to three-hour infusion of 2.5 per cent saline increases it to 9.7 per cent [*4*].

It may again be posited that prehydration leaves an inhibitory effect in the antinatriuretic system (D, Fig. 2) which remains subliminal, so that after the eight to thirteen hour interval sodium excretion is only slightly increased. Again, however, we suppose that this inhibitory effect undergoes progressive potentiation with the consequence that when a second inhibitory effect is imposed by the rapid administration of saline, inhibition becomes functionally effective and marked natriuresis ensues. Hence, infusion of saline eight to thirteen hours after prehydration induces not only maximal water diuresis but also (near?) maximal natriuresis.

An alternative explanation for the natriuresis induced by saline in prehydrated subjects might be sought in the interpretation of Wrong [*154*] who finds that when sustained hydration is produced by the administration of pitressin and water, sodium excretion increases slowly to reach a maximal rate (125 to 200 μEq./minute) six to twelve hours after hydration. (We estimate the maximal excretion fraction to be 0.7 to 1.2 per cent, roughly equivalent to Ladd's average preinfusion value in prehydrated subjects of 1.7 per cent.) Wrong suggests that this delayed natriuresis is due to the slow disappearance of aldosterone from the circulation. This interpretation, however, fails to explain why the average peak excretion fraction in prehydrated subjects should increase to 8.8 per cent when saline is infused eight to thirteen hours later unless one posits that aldosterone secretion persists at a reduced level after prehydration and is further inhibited by saline infusion; or alternatively, that the challenging infusion of saline brings about the cessation of secretion of some other antinatriuretic hormone far more potent than aldosterone itself. Nor does Wrong's interpretation explain why a two- to three-hour infusion of 2.5 per cent saline leads to an excretion fraction of 9.7 per cent. Neither is it clear why the progressive destruction or excretion of any sodium-retaining steroid would so markedly increase the "inhibition" of the antidiuretic system effected by a challenging infusion of saline.

A biologically warranted question phrased in teleologic terms may be asked here: would a subliminal but progressively intensified inhibition in the antidiuretic and antinatriuretic systems be useful to the organism? Our immediate answer would be yes, to the extent that it would perhaps enable the organism to cope with successive, closely related episodes of water or salt loading more effectively. Rembering that, with water available *ad lib.*, salt loading leads to (isotonic) water loading, we are encouraged to look for related phenomena after salt loading *per se*, a matter on which there is little information unless the observations of Birchard and Strauss, discussed later, are so construed.

EFFECTS OF SECOND HYDRATION

One more feature of Ladd's experiments remains to be discussed. The diuresis induced by

* In the first instance we have visualized expansion of the body fluids as merely reducing excitation of the antinatriuretic system (B, Fig. 2), as osmotic dilution of the body fluids is presumed to reduce excitation of the osmoreceptors in the antidiuretic system (A, Fig. 1), but for heuristic purposes "cessation of excitation" and "active inhibition" may be considered to be physiologically equivalent.

saline in prehydrated subjects is not substantially reduced when the saline is infused immediately after the ingestion of a second load of water (1.5 to 2.5 L. in fifteen to sixty minutes) * or early in the ensuing diuresis; but if the saline is infused later in the second diuretic response, the saline produces progressively less diuresis until—when administered at the tail-end of the second diuretic response—the saline-induced diuresis is nearly abolished. Thus it appears that a second episode of hydration abolishes the effects of the first (prehydration) episode. Perhaps we might speak here of "inhibition of inhibition" if this were not overburdening otherwise potentially useful words. If it is asked why a second episode of hydration (remembering that hydration is normally *not* an inhibitory stimulus to the antinatriuretic center) should erase the "inhibition" which follows the initial prehydrating episode, it can only be noted that the initial "inhibitory" phenomenon was engendered by hydration in the beginning and itself remains unexplained. (Detailed data on the magnitude of natriuresis after a second episode of hydration are unfortunately not available.)

OTHER EXAMPLES OF POSSIBLE CENTRAL SUMMATION

A few other experimental procedures bear upon this topic. Birchard and Strauss [*10*] showed that if "normal" subjects are preloaded orally with saline (about 3 L.) *the day before testing*, then the ingestion while sitting up of isotonic saline (1 L.), which ordinarily has no such effect (see First Year Class experiment), leads to a very good (although not maximal) diuresis (5 to 8.9 cc./minute). Moderate hydropenia tends to off-set this diuretic response, probably by enhancing neurohypophysial activity. Birchard and Strauss suggest that preloading with saline leaves the extracellular fluid volume significantly expanded the next day; this is doubtless true; but why, then, is not an equivalent diuresis induced simply by infusing 2 or 3 L. of saline? It is possible that preloading with saline between −twenty-four and −sixteen hours leaves much the same subliminal inhibition in the antidiuretic system as preloading with water at −eight to −thirteen hours. (It is noteworthy, however, that preloading with saline did not enhance sodium excretion during the challenging dose of saline the next day; either any tendency toward natriuresis was offset by orthostasis or inhibition of the antinatriuretic system is more specifically related to hydration of the body than to expansion of the extracellular fluid.)

Birchard and Strauss [*10*] also report that isotonic saline induces moderate diuresis (3.3 to 5.9 cc./minute) in *sitting* subjects when ingested on the descending limb of water diuresis (1 L.), but not in non-hydrated sitting subjects. Again, since large volumes of saline do not have this effect, summation of fluid volumes, as suggested by the authors, seems less likely than summation of inhibitory effects.

Conversely, Birchard et al. [*9*] have shown that drinking 1 L. of water induces diuresis in supine subjects when administered on the descending limb of hypertonic saline diuresis (1 L. of 2 per cent saline intravenously), at a time when the plasma sodium concentration (and presumably osmotic pressure) is still elevated and therefore predisposing to antidiuresis. However, since the extracellular fluid is not only expanded but also hypertonic, the addition of water to this fluid may simply expand it further and tip the scales in favor of diuresis, even as isotonic saline does in supine subjects. Anomalous phenomena such as this have hitherto been offered as evidence of "adaptation" in the osmoreceptor system; Birchard, Rosenbaum and Strauss [*9*] review the literature on this subject, and the possibility of true adaptation cannot be lightly dismissed. However, "adaptation" implies an immediate change in threshold of excitability with respect to the primary stimulus, whereas the phenomena discussed here are generally not of this nature—for example, neither diuresis nor marked natriuresis are present in the interval eight to thirteen hours after prehydration, but remain to be "uncovered" or induced by the "summation" of what are presumably inhibitory effects, one of which remains subliminal until the second is superimposed.

RES INCERTAE

There remain several observations which our syllogism cannot pretend to cover. Some years ago Hickey and Hare [*66*] utilized a combination of water diuresis and intravenous hypertonic saline (infusion of 2.5 per cent saline at 0.25 cc./minute per kg. for forty-five minutes after 20 cc./kg. of tap water *per os*) as a diagnostic

* The simultaneous administration of water and hypertonic saline leads only to antidiuresis, with no excessive excretion of sodium [*8,66*].

test for diabetes insipidus. Dr. Thomas Findley has entertained the possibility that the neurohypophysis may be involved in that still mysterious melange known as hypertensive vascular disease, and to test the functional integrity of this organ he and his collaborators [*8*] explored the effects of a modified Hickey-Hare test on, first, "normal" volunteers, and second, on patients with hypertensive vascular disease. The volunteers reacted to the Hickey-Hare test much as do all "normal" subjects—nothing very much happened; the hypertonic saline produced antidiuresis despite the ingested water and the excretion fraction of chloride in ten subjects increased to an average of 3.7 per cent, exceeding 5 per cent in only one subject. It is unnecessary to dwell on the now frequently demonstrated fact, first recorded by Farnsworth [*47*] in 1943, that in response to a challenging infusion of saline, subjects with hypertensive vascular disease respond with natriuresis substantially exceeding that observed in normotensive subjects; the maximal excretion fraction in eight hypertensive patients tested by Findley and his colleagues averaged 10.1 per cent, reaching 15.1 per cent in one patient.* These investigators also tested one patient with Cushing's syndrome, who responded with the phenomenal excretion fraction of 21 per cent.

A pair of endocrine glands, located just above the kidneys, have long been thought to have (among other functions) something to do with the renal conservation of sodium. I [*127*] have noted that in 1951, 1952 and 1953, approximately 14,598 papers were published on these glands, and we still do not know anything much about them except that they somehow promote the tubular reabsorption of some fraction of the filtered sodium and that, in their absence, as Loeb and his colleagues showed many years ago, excessive loss of sodium in the urine leads to depletion of the extracellular fluid. Pharmaceutical firms have made available several preparations possibly related to the physiologic action of these glands, and Findley and his collaborators observed the effects of some of these preparations on a "normal" subject. DOCA® produced an equivocal excretion fraction of 3.7 per cent after hypertonic saline; ACTH (intravenously) increased this to 6 per cent; and pretreatment combined with simultaneous treatment with cortisone (200 mg. at—two days; 100 mg. at—one day; 100 mg. at zero time) increased it to 8 per cent. (Fig. 3.)

It seems, then, that (1) prehydrated normotensive subjects, (2) subjects with hypertensive vascular disease, (3) the *one* patient with Cushing's syndrome who has been examined, and (4) normotensive subjects pretreated with ACTH or cortisone, have one or more features in common which lead to excessive sodium excretion when the body fluids are abruptly expanded with saline (and perhaps other) infusions. Taking typical figures, the result is that the sodium excretion fraction, usually less than 1 per cent, increases to 3 per cent in "normal" subjects after body fluid expansion, and to nearly 10 per cent in the various circumstances enumerated above. These figures correspond to some 11, 33 and 108 gm. of sodium chloride per day. If changes in filtration rate can confidently be excluded as causally related to increased natriuresis (as we believe to be the case in the studies cited) then the explanation of the latter must be sought in the factors that determine the tubular reabsorption of sodium.

In any case, when we discover what feature or features (1) prehydration, (2) hypertensive vascular disease, (3) Cushing's syndrome, and (4) cortisone treatment have in common, we may have a monkey wrench on the physiologic mechanism(s) which controls the sodium content of the body, and which, when tampered with in the circumstances reviewed here, permits the excretion of sodium at a rate that, if continued, would deplete the body of sodium chloride in a day, more or less. If we ever do get our hands on such a monkey wrench we may have to use it carefully lest we have to infuse the patient's own urine back into his veins [*1,34*] as a therapeutic life-saving measure.

CENTRAL REPRESENTATION OF THE ANTINATRIURETIC SYSTEM

The central representation of the antidiuretic system in the hypothalamic-neurohypophysial tracts is well established. With respect to sodium

* Excessive natriuresis in hypertensive subjects does not seem to be specifically related to the infusion of sodium because it can be induced by the infusion of mannitol [*19*], isotonic glucose [*40*], isotonic saline with PAH and inulin (2 cc./minute) [*4*], and even by catheterization [*94*]. The only warrant for including hypertensive subjects in this list is that they supply additional evidence that the antinatriuretic system is a labile one. Saline infusions frequently increase the filtration rate in hypertensive subects, but their excessive natriuresis under provocation is apparently not solely related to this fact. Baldwin et al. [*4*] find that it is not related to any obvious defect in the kidneys and attribute it to an extrarenal origin.

conservation, it is conceivable that a humoral agent might be transmitted from receptors, however constituted and wherever located, directly to the kidneys without a central integrating mechanism; but it is equally plausible to believe, on the phylogenetic grounds previously stated, that a central mechanism permitting integration may be located in the brain stem.

Various lesions in the neuraxis have been said to be accompanied by disturbances in sodium balance, but such lesions are generally widespread and, in the absence of more detailed studies on diuresis and natriuresis under controlled conditions, throw little light on the present problem. It has been remarked that one of the strongest lines of evidence against the belief that sodium balance critically involves an integrating system in the neuraxis is that no lesion is known which causes an excessive excretion of sodium. This argument, however, fails to be convincing because of its negative nature. What is here called the antinatriuretic system presumably controls only part of sodium reabsorption and its action may be replaced, in event of impairment, by compensatory function in the kidney or elsewhere.

In the absence of indications to the contrary, we would not look to the telencephalon (primitively concerned with smell) or the mesencephalon (primarily concerned with somatic segments anterior to the mouth, and notably the eye muscles and optic lobes) for this representation. The hind-brain (medulla and pons) is a possibility; although concerned with the mouth, respiration, temperature control, vestibular apparatus and neuromuscular co-ordination, this segment of the brain stem is also concerned with vasomotor regulation, a function closely related to body fluid regulation. On the other hand, the diencephalon seems to be a better possibility because of the location here of the antidiuretic system and the close relation of the median eminence and infundibular stalk to the adenohypophysis.

Where the neurohypophysis is a down-growth from the floor of the third ventricle, the adenohypophysis is an up-growth from the roof of the mouth; in establishing its ultimate anatomic relation with the infundibular stalk, the adenohypophysis has lost most of the innervation and primary arterial blood supply it once may have had, and now remains virtually without a nerve supply and dependent for its blood largely upon a portal system, the blood of which is derived from the capillaries of the median eminence and infundibular stalk in the floor of the third ventricle.

Wise [*153*] reports that stimulation of the caudal portion of the floor of the fourth ventricle in the dog increases sodium excretion, but if this region is critically involved, the localization of excitation is not sufficiently sharp to yield consistent effects. Moreover, the possibility of an increase in filtration rate must be ruled out, especially since the experimental lesions are close to the vasomotor center. On the other hand, Rauschkolb and Farrell [*113*] report that aldosterone excretion is not decreased by decortication or transection of the spinal cord, sympathetic trunks and vagi; but it is decreased by decapitation or decerebration just posterior to the diencephalon, indicating that some area in the latter exercises an influence on aldosterone secretion by the release of a circulating hormone. No *a priori* contradiction can be argued for these two series of observations, and there is no *a priori* reason to identify the antinatriuretic system as postulated here with a center controlling aldosterone secretion.

As we have emphasized, the precise control of sodium balance must be very old, probably dating back to the earliest fresh-water vertebrates (or provertebrates). (The neuraxis is well preserved in a fossil Devonian ostracoderm, *Cephalaspis*, and has a structure wholly similar in its major segments to that of primitive recent fishes [*56*].) This circumstance leads to the speculation that a primeval antinatriuretic hormone, X, may have been secreted by some part of the neuraxis before the adenohypophysis and adrenal cortical tissue acquired their importance in sodium balance. We conceive that the secretion of X was evoked by reduction in the volume of body fluid and, carried directly to the kidneys, enhanced the tubular reabsorption of sodium by the primitive nephron. As adrenal cortical tissue evolved and additional (peripheral) humoral agents became available to promote sodium reabsorption (perhaps only in a more or less constant or "obligatory" manner, or in relation to ion exchange mechanisms), X may have continued to serve as the active agent effecting rapid or facultative changes in tubular reabsorption, and the secretory activity of the adrenal cortex itself may have come in part under its control. (I am not aware of evidence that changes in adrenal cortical secretion are directly responsible for such rapid changes in

tubular reabsorption as have been discussed here, even though aldosterone secretion appears to be enhanced by circumstances which reduce the volume of the body fluids [*6*].) When the adenohypophysis came into anatomic relation with the infundibular stalk and into humoral dependence on the hypothalamic-adenohypophysial portal system, X itself may have come to serve as a secretory stimulus to adenohypophysial hormones such as ACTH, which supplemented it in the regulation of the secretion of sodium-conserving adrenocortical agents.

These speculations, which are all they pretend to be, would lead us to look for the central representation of the antinatriuretic system in the brain stem, and perhaps in the hypothalamus; and for a neurohumoral agent that (1) has a direct antinatriuretic effect on the renal tubules and (2) that may act as a tropic or secretory stimulus to the adrenal cortex and possibly (?) to the adenohypophysis. The discovery of such an agent would go far to explain an increasing body of evidence that patients with Addison's disease or bilateral adrenalectomy, when receiving supportive therapy in the form of excess sodium chloride and cortisone, and patients with panhypopituitary deficiency or after total hypophysectomy, can effect many of the rapid adjustments in sodium excretion characteristic of the normal subject [*115*].

SUMMARY

The literature has been reviewed with respect to the effects of changes in volume of the body fluids on the excretion of water (diuresis) and sodium (natriuresis). Renal conservation appears to be effected by humoral agents which promote the tubular reabsorption of (osmotically free) water, on the one hand, or sodium, on the other, and hence the controlling physiologic mechanisms have been designated the "antidiuretic" and "antinatriuretic" systems, respectively.

It is well established that the antidiuretic system has central representation in the diencephalon, comprising receptors (osmoreceptors), intercalated or internuncial paths (supraoptico- and paraventriculo-hypophysial tracts) and a humoral effector agent (antidiuretic hormone).

It is commonly accepted that water balance is primarily conditioned by the osmotic pressure of the body fluids, but abundant evidence shows that the antidiuretic system is subject to excitation and inhibition by neural pathways or agents acting independently of osmotic pressure (the only such agent emphasized here is alcohol, which affords an illustration of inhibition), and presumably the activity of this system at any moment reflects the algebraic summation of several such excitatory and inhibitory stimuli.

Attention is called to the recent demonstration by Henry, Gauer and their colleagues that increased distention (diastolic volume) of the left atrium (and possibly the pulmonary veins within the pericardium) affords afferent vagal impulses which appear to induce diuresis by inhibition of the antidiuretic system. The diuresis induced by the change from sitting to supine position, the infusion of isotonic saline solution, iso-oncotic and hyperoncotic albumin solutions in the supine position (and possibly by the inhalation of 5 to 7 per cent carbon dioxide) may tentatively be interpreted as reflecting an increase in the inhibition of the antidiuretic system imposed by the left atrial reflex. Conversely, the antidiuresis associated with hemorrhage, orthostatic circulatory insufficiency, occlusion of venous return by pressure cuffs or vena caval obstruction, and the sitting position, are interpreted as reflecting a decrease in the inhibition imposed by the left atrial reflex. The tentative acceptance of the left atrial hypothesis does not exclude the existence of other volume-sensitive receptors having functional relations with the antidiuretic system.

The factor or factors controlling sodium conservation are unknown, but the evidence indicates that among them is either the volume of the extracellular (interstitial) fluid (as proposed by Strauss and his collaborators), or the degree of filling of the arterial tree (as proposed by Epstein and his collaborators). Whatever the location of the receptors, it is proposed that the antinatriuretic system presents a similar pattern of receptors, internuncials, and at least one humoral effector agent which promotes sodium reabsorption by the renal tubules, and that this antinatriuretic system, like the antidiuretic system, has central representation (perhaps in the diencephalon) and is the locus of algebraic summation of excitatory and inhibitory stimuli.

When a challenging infusion of saline solution is given to subjects who have been prehydrated (massive water diuresis) eight to thirteen hours previously, this saline induces marked diuresis and natriuresis, responses which are not observed in non-prehydrated subjects. It is suggested that these responses reflect a subliminal, progressively

increasing "inhibition" (the word is used in a qualified sense) in both the antidiuretic and antinatriuretic systems, this subliminal inhibition reaching its maximal development after eight to thirteen hours at which time a second inhibitory stimulus (isotonic saline), which ordinarily has only a slight inhibitory effect on either system, now produces approximately complete inhibition of both systems with, consequently, maximal diuresis and possibly near maximal natriuresis. Other phenomena which can be interpreted as reflecting the central summation of inhibitory phenomena in the antidiuretic (and possibly the antinatriuretic) system are cited.

The antidiuretic and the antinatriuretic systems may apparently be excited and inhibited wholly independently of each other; but at any specific level of antinatriuretic activity, the antidiuretic system operates rapidly to promote the conservation or excretion of water in such a manner as to maintain the osmotic concentration of the body fluids at a fixed constant value (about 283 $\pm$ 11 mOsm./L.), regardless of body fluid volume. In consequence of this final integration, the osmotic pressure of the body fluids is one of the most closely regulated of all homeostatic states and tends to take precedence over volume regulation.

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Seminar on Atherosclerosis

The Genetic Aspects of Atherosclerosis*

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Atherosclerosis as manifested by coronary heart disease has been known to run in some families, but whether this familial prevalence is the result of nature or of nurture has generally not been clear. There appear to be many disorders which predispose to the development of atherosclerosis, some of which are thought to be, in part at least, genetically determined. For most of these, however, we have very little knowledge of the method of inheritance. Diabetes, for instance, predisposes to the development of coronary heart disease and appears to be in large part genetically determined, but as yet there is no definite agreement as to how it is inherited. Hypertension is a similar factor.

The relationship of lipid metabolism to atherosclerosis is of more interest because of the close association between the levels of serum lipids and coronary heart disease. At the present time little is known concerning genetic mechanisms which might affect serum cholesterol levels within the so-called "normal" range. Since the great majority of persons with atherosclerosis have cholesterol levels within this range, such mechanisms, if they exist, would be of great importance. However, the effects of diet, hormones and disease on cholesterol levels are such as to obscure all but rather striking differences and make such studies difficult to evaluate.

Disorders of lipid metabolism have been found to predispose patients to coronary heart disease. Although these disorders are not common, they are of interest because of the light they may shed on the problem of atherosclerosis as a whole. Of two lipid disorders known to be familial the method of inheritance has in one instance been well established. Idiopathic hyperlipemia occurs in families and is probably genetically determined. At present there are not enough data available to warrant any conclusion concerning the mode of inheritance. However, familial hypercholesterolemic xanthomatosis has been carefully studied, and it is the purpose of this paper to review the genetics of this disorder and to present further data bearing on the mechanism by which it is inherited.

Familial hypercholesterolemic xanthomatosis is characterized by an elevated level of serum cholesterol, a clear (not milky) serum, tendon nodules (xanthoma tendinosa), skin xanthoma (xanthoma plana and tuberosa) and xanthelasma. Other lipid abnormalities which are found less constantly include elevations of cholesterol: phospholipid ratios, Sf_{12-20} and Sf_{20-100} lipoproteins and beta lipoproteins. It has long been recognized that hypercholesterolemia may be the only manifestation of this disorder but the frequency with which xanthomatous lesions are found has generally been underestimated. Piper and Orrlid [*1*] in a study of twelve families with this disorder concluded that in 80 per cent of their patients tendon lesions would eventually develop. In our study, the clinical details of which will appear in a subsequent publication, 54 per cent of sixty-nine persons had tendon lesions and of those over forty years of age 91 per cent were so affected. These studies suggest that in most persons with familial hypercholesterolemic xanthomatosis tendon xanthoma will eventually develop. Xanthelasma, skin xanthoma and arcus senilis are much less common in our experience, being found in 26.1 per cent, 7.2 per cent and 5.6 per cent of our patients, respectively. Coronary heart disease has been known to occur with great frequency in these patients. We found it in 27.5 per cent of ours and in 65.3 per cent of those over forty years of age. Atherosclerosis is an almost inevitable consequence of this disorder.

Hypercholesterolemic xanthomatosis has generally been considered to be an inherited dis-

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order and two genetic mechanisms have been proposed to account for its familial prevalence. A number of investigators, including Muller [2], Alvord [3], Svendsen [4], Wheeler [5], Piper and Orrlid [1], and Leonard [6], have attributed this prevalence to simple Mendelian dominance,

TABLE I
SERUM CHOLESTEROL LEVELS OF 146 HEALTHY MEN ACCORDING TO AGE

Age (yr.)	No.	Cholesterol (mg. %)		
		Mean	S.D.	Mean + 2 S.D.
20–29	20	195	41.1	277
30–39	74	224	41.3	307
40–59	52	238	40.8	320

* S.D. = Standard Deviation.

whereas Boas and Adlersberg [7], Adlersberg [8], and Wilkinson [9] have suggested that the disorder is inherited as an incompletely dominant trait, the heterozygous state being represented by hypercholesterolemia alone, the homozygous state by hypercholesterolemia and xanthoma.

We have investigated the clinical features and prevalence of hypercholesterolemic xanthomatosis in twelve families by the methods described herein. A genetic analysis of these data follows.

METHODS OF STUDY

One hundred and eighty relatives of twelve unrelated persons with hypercholesterolemic xanthomatosis were examined. These 192 persons were selected and studied and the data analyzed by the following methods.

Hypercholesterolemia was defined as a serum cholesterol level greater than the mean plus two standard deviations of a control group. This value was chosen as the upper limit of normal because statistically only 5 per cent of a normal population might be expected to exceed this level. The control group consisted of 146 healthy men from twenty to fifty-five years of age who had previously been studied in this laboratory (Gertler, Garn and Bland [10]). The values for three age groups of this control series are listed in Table I and are similar to those reported by Keys and associates [11] for normal males in Minnesota. The serum cholesterol levels for persons older or younger than the control group were compared with the nearest age group. Thus hypercholesterolemia was defined without recourse to the results of this study.

A diagnosis of hypercholesterolemic xanthomatosis was made only in persons who presented one of two groups of findings as follows: (1) hypercholesterolemia, a clear serum and tendon nodules; a combination of findings which we will refer to as the "full syndrome," or (2) hypercholesterolemia, a clear serum and a parent or sibling who had the "full syndrome." Persons who had hypercholesterolemia,

TABLE II
THE PREVALENCE OF HYPERCHOLESTEROLEMIA IN THE CHILDREN AND SIBSHIPS OF PERSONS WITH HYPERCHOLESTEROLEMIC XANTHOMATOSIS ACCORDING TO AGE

Age (yr.)	No.	Hypercholesterolemics		P
		No.	%	
0–19	44	23	52.3	
20–39	47	23	49.0	.70
40+	28	17	60.7	
Totals	119	63	52.8	

NOTE: These 119 are the 68 children and 51 siblings used in the genetic calculations and found in Figs. 1 and 3.

TABLE III
THE PREVALENCE OF TENDON NODULES IN THE HYPERCHOLESTEROLEMIC CHILDREN AND SIBLINGS OF PERSONS WITH HYPERCHOLESTEROLEMIC XANTHOMATOSIS ACCORDING TO AGE

Age (yr.)	No.	With Tendon Nodules		P
		No.	%	
0–19	23	4	17.4	
20–39	23	12	52.2	.01
40+	17	15	88.3	
Totals	63	31	49.3	

but whose siblings or parents were not known to have the "full syndrome" were not classified as having this disorder.

Is this second type of classification justified? Do hypercholesterolemic children and siblings of persons with the "full syndrome" have this disorder as previous investigators have assumed? The results of this study support this concept. In Table II the prevalence of hypercholesterolemia in the children and siblings of persons with hypercholesterolemic xanthomatosis is listed according to their ages and indicates that the prevalence does not increase with age. In Table III the prevalence of tendon nodules is also listed according to

the ages of these hypercholesterolemic children and siblings. Below the age of twenty years only 17.4 per cent of these hypercholesterolemic persons had tendon nodules, whereas over the age of forty years, 88.3 per cent were so affected. This strongly suggests that in those individuals with hypercholesterolemia alone the "full syndrome" will eventually develop. Thus we believe that the second definition of this disorder is a generally valid one.

The twelve index cases were consecutive unrelated patients with the "full syndrome" who were seen on the wards of the Massachusetts General Hospital or as private patients. All had hypercholesterolemia, a clear serum and tendon nodules. In addition, eight had coronary heart disease, eight had xanthelasma, three had skin xanthoma and one had a corneal arcus.

An attempt was made to examine the close relatives of these index cases who were living in the Boston area. The children and siblings of normal relatives were not regularly studied. Children below the age of six years were not asked to cooperate, but at the parent's request these children were examined. One child and two adults refused to be examined. No statistics are included in the data on persons who were dead at the time of the study except in Table VI where they are used to determine birth order. Although the twelve patients were not selected because it was known that they had relatives with this disorder, it is possible that patients whose relatives had the same disorder would be more likely to seek medical attention and to cooperate in such a study.

All 192 persons in this study were examined by me. Most of these people were examined in their homes. The examination consisted of a history and physical examination recorded on a mimeographed form, a urine examination for sugar and albumin, a determination of serum cholesterol, determination of Sf_{12-20} and Sf_{20-100} serum lipoproteins, an electrocardiogram and blood typing. Fluoroscopic or roentgenographic examination of the heart was made on persons seen in the office or hospital. Although in some instances there were multiple determinations of serum cholesterol, only the first determination is reported in this paper so that the method of reporting is consistent for the entire study.

Serum cholesterol was determined according to the methods of Bloor [12]. In the analysis of the data and their statistical significance, standard statistical methods were used. These included standard error of the difference between means, standard error of the difference between proportions, and chi square with correction of Yates for small numbers. Calculations of expected numbers of affected persons among the siblings of persons with the disorder were made according to the method of Hogben [13].

RESULTS

The Familial Prevalence of Hypercholesterolemic Xanthomatosis. The prevalence of hypercholesterolemia in the children of parents with this disorder is compared with its prevalence in the children of parents without the disorder. (Figs. 1 and 2). In the twenty-five families in which one parent had hypercholesterolemic xanthomatosis, thirty-four children or 50 per cent had hyper-

FIG. 1. The prevalence of hypercholesterolemic xanthomatosis among children of parents with this disorder.

cholesterolemia. Of twenty-four children from eleven families in which no parent had the disorder, one had hypercholesterolemia. These data are in accord with the prevailing belief that hypercholesterolemic xanthomatosis is a familial disorder.

The Method of Inheritance of Hypercholesterolemic Xanthomatosis. The data from this study have been analyzed to see if the observed familial prevalence of the disorder is in keeping with any known genetic mechanism. Two groups of fami-

lies were analyzed for this purpose: Group I, families in which a parent was the "index case," i.e., the person through whom the other members of the family were located, and Group II, families in which a child was the index case.

In group I, there were twenty-five families in which a parent who had hypercholesterolemic xanthomatosis was the index case. (Fig. 1.) In fifteen of these families both parents were alive and were examined. In each family one parent had the "full syndrome" and the other did not have the disorder. Of the latter, four had hypercholesterolemia but no known relatives with hypercholesterolemic xanthomatosis and are assumed to be normal in this respect. Of forty children, eighteen or 45 per cent had hypercholesterolemia and of these two had the "full syndrome."

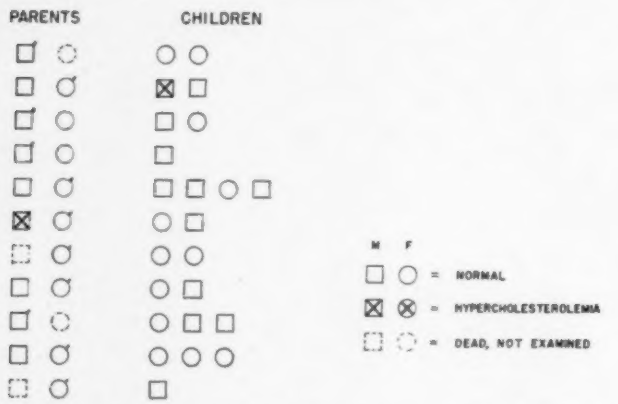

Fig. 2. The prevalence of hypercholesterolemia among children of normal parents.

There were ten families in which the data concerning the parents were less complete. In three of these the index parent had the "full syndrome," but the other parent was dead or, in one case, uncooperative; of six children four had hypercholesterolemia. In another three families the index parent had hypercholesterolemia and siblings with the "full syndrome," the other parent was normal: one of six children had hypercholesterolemia. In the last four families the index parent was dead but had living siblings with the "full syndrome." In one of these families there was a reliable history of tendon nodules in the index parent, and in the other three the index parents had died of probable coronary disease in their forties. It is assumed that these four parents had the disorder. Of sixteen children, eleven were hypercholesterolemic five of whom had the "full syndrome."

Summary of these data, from the twenty-five families in which a parent with hypercholesterolemic xanthomatosis was the index case, shows that thirty-four of sixty-eight children (50 per cent) had this disorder.

Are these results in keeping with any genetic mechanism? If the disorder was inherited as a simple Mendelian dominant and only one parent was affected, 50 per cent of the children would be expected to have the disorder. The only other mechanism which could have produced this prevalence in the children would be one in which the disorder represented the homozygous state while the heterozygous state produced no recognized abnormality, with the assumption that the unaffected parent in each family was heterozygous for this disorder. The latter explanation seems most unlikely.

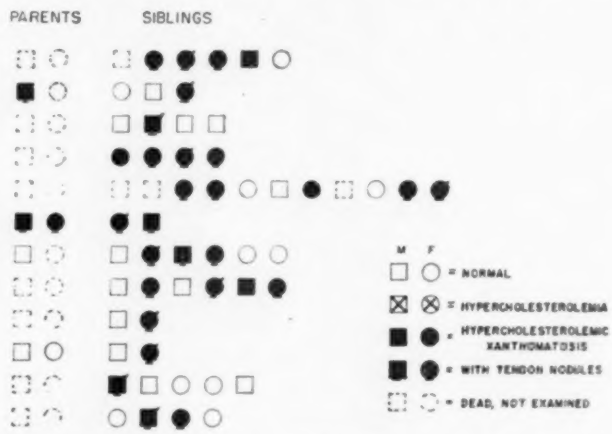

Fig. 3. The prevalence of hypercholesterolemic xanthomatosis among siblings and parents of persons with this disorder.

In group II, there were twelve families in which the index case was a child with the full syndrome. (Fig. 3.) The data from these families have been analyzed with regard to the prevalence of the disorder among the siblings of these children. In ten of these families data about the parents is incomplete: in eight both parents were dead, in one the living parent was normal and in one the living parent had the "full syndrome."

Does the number of siblings with the disorder follow the pattern of simple Mendelian dominance suggested by the data from the children of affected parents? In Table IV a calculation has been made of the number of siblings who might be expected to have the disorder in these ten families, assuming first that the disorder is inherited by simple Mendelian dominance and secondly that only one parent has the disorder. The latter assumption is reasonable in the

presence of an uncommon disease. This calculation is made according to the method of Hogben [*13*] which takes into account the fact that families with no affected children can not be found by this type of selection. Of the forty-seven siblings, twenty-six had the disorder whereas the expected number was 24.7. This difference between the observed and expected numbers is not statistically significant. Thus the data from these ten families also fit the pattern of simple Mendelian dominance.

TABLE IV
COMPARISON OF OBSERVED AND EXPECTED NUMBERS OF SIBLINGS WITH HYPERCHOLESTEROLEMIC XANTHOMATOSIS ASSUMING SIMPLE MENDELIAN DOMINANCE AND ONE PARENT AFFECTED

Sibship Size	Sibship No.	No. of Affected Siblings Observed	No. of Affected Siblings Expected*
1	0	..	......
2	1	1	1.333
3	1	1	1.714
4	3	7	6.399
5	2	5	5.162
6	2	7	6.094
7	0	..	......
8	1	5	4.016
Totals	10	26	24.718

NOTE Significance ratio t = 0.45.
* Calculated according to formulas in reference 13.

There were two of the twelve families in which both parents were living. In one of these both parents had the "full syndrome" and both children had the disorder. In the second family both parents were normal and one of the two children had the "full syndrome." This last observation is not consistent with the mechanism of simple dominance since one parent would be expected to have the disorder. There are several possible explanations for this finding: (1) the disorder is present in one of the parents but not manifest due to lack of "penetrance" or other factors, (2) there has been illegitimacy, or (3) mutation has occurred. This last seems unlikely since distant relatives have the disorder. Illegitimacy cannot be proved by the blood types. There is no information available bearing on the question of penetrance. Thus there is no adequate explanation for the findings in this one family.

The foregoing analysis indicates that hypercholesterolemic xanthomatosis is inherited as a simple Mendelian dominant trait.

The Prevalence of Hypercholesterolemic Xanthomatosis According to Sex. The family data have been analyzed with regard to the relationship between sex and the prevalence of the disorder. (Table v.) Among the sixty-eight children of parents with the disorder there were forty-two males and twenty-six females, of whom twenty-four males and ten females had the disorder. These numbers do not differ significantly from the expected ratios of 50 per cent. In the families in which a child with the disorder was the index case, twenty-two of thirty-two females and seven of nineteen males had the disorder. In this group there appear to be too many females with the disorder. This may be explained by the fact that in nine of these twelve families a woman with the disorder was the index case. Totaling all these data we find that thirty-one of sixty-one males and thirty-two of fifty-eight females had the disorder. Thus there was no evidence that the disorder was sex limited or sex determined in these families.

TABLE V
THE PREVALENCE OF HYPERCHOLESTEROLEMIC XANTHOMATOSIS AMONG THE CHILDREN AND SIBSHIPS OF PERSONS WITH THIS DISORDER ACCORDING TO SEX

	Males		Females		
	No.	% With Disorder	No.	% With Disorder	P
Children of parents with the disorder..	42	57.2	26	38.5	.30
Sibships of persons with the disorder..	19	36.9	32	68.8	.01
Totals............	61	50.8	58	55.2	.70

The Prevalence of Hypercholesterolemic Xanthomatosis According to Birth Order. The data have also been analyzed with regard to a possible relationship between birth order and the prevalence of hypercholesterolemic xanthomatosis. For this purpose both family groups have been combined and dead siblings have been used for the purpose of determining birth order. (Table VI.) There

appears to be no association between birth order and the prevalence of this disorder.

Ethnic Origin and the Prevalence of Hypercholesterolemic Xanthomatosis. There was no evidence that any particular racial group was prone to have this disorder. In these twelve families the following racial backgrounds were represented: English (1), German and English (1), Scotch and English (1), Scotch (1), Irish (1), Syrian (1), Jewish (3) and French Canadian (3). This is in accord with previous reports which indicate that the disorder is not confined to any particular racial group.

TABLE VI
PREVALENCE OF HYPERCHOLESTEROLEMIC XANTHOMATOSIS IN THE CHILDREN AND SIBSHIPS OF PERSONS WITH THIS DISORDER ACCORDING TO BIRTH ORDER

Birth Order	No. Persons	No. Persons with Disorder	Per cent with Disorder
1	35	15	42.8
2	32	20	62.6
3	22	12	54.7
4	13	7	53.8
5	9	5	55.7
6	4	1	25.0
7	1	1	100.0
8	0	0	.....
9	1	0	0.0
10	1	1	100.0
Totals	119	63	52.8

NOTE: $X^2 = 2.52$. N = 4 p = 0.50.

COMMENTS

The foregoing analysis of the genetics of hypercholesterolemic xanthomatosis indicates that hypercholesterolemia is inherited as a simple dominant state. The appearance of tendon xanthoma and other clinical manifestations of the disorder is dependent upon age and the level of serum cholesterol. This is in agreement with the studies of many investigators. However, Boas and Adlersberg [*7,8*] and Wilkinson [*9*] have suggested that hypercholesterolemia represents the heterozygous state, the homozygous state being represented by xanthoma. That such was not the case in the present study is indicated by consideration of the following points. In the first place, the genetic data do not permit such a hypothesis. Of forty-six children of eighteen parents who had the "full syndrome," twenty-four had normal cholesterol levels. There were two families in which one parent had the "full syndrome" and the other parent was normal, but in which two of the four children had the "full syndrome." If the theory of incomplete dominance was correct for these families, all the children in the first type of family should be hypercholesterolemic, while in the second type of family none should have the "full syndrome."

In the second place, although the prevalence of hypercholesterolemia is not related to age in the children or siblings of persons with this disorder, the prevalence of tendon nodules increases with age. (Tables II and III.) Thus of the 119 siblings and children of persons with hypercholesterolemic xanthomatosis used in the genetic calculations, hypercholesterolemia was found in 52.3 per cent of those zero to nineteen years of age, in 49 per cent of those twenty to thirty-nine years of age, and in 60.7 per cent of those forty years of age or more. However, of these sixty-three siblings and children with hypercholesterolemia, tendon nodules occurred in only 17.4 per cent of those zero to nineteen years of age, in 52.2 per cent of those twenty to thirty-nine years of age, and in 88.3 per cent of those forty years of age or more. Furthermore, the prevalence of tendon nodules increases with the height of the serum cholesterol level.

For these reasons the hypothesis of incomplete dominance does not appear to apply to this disorder as observed in this study. The primary manifestation appears to be hypercholesterolemia which is present in early life, while the appearance of secondary manifestations such as tendon nodules, xanthelasma, skin xanthoma and coronary artery disease are dependent upon time and the severity of the lipid abnormalities.

Are these results at odds with those obtained by Boas and Adlersberg and by Wilkinson? In their studies it was agreed that hypercholesterolemia was inherited as a simple dominant trait, but they believed that xanthoma appeared only in the presence of the homozygous state. Boas and Adlersberg give information for thirty-five families [*7*]. There were five matings in which a person with the "full syndrome" had children. Of the nine children, three had normal serum cholesterol levels according to their criteria, rather than the hypercholesterolemia demanded by their hypothesis. There were two matings in which both parents had hypercholesterolemia. Of six children, three had xanthoma, two had hypercholesterolemia and one was normal. These numbers are too small to permit

valid conclusions. Thus their data are inconsistent with the hypothesis of incomplete dominance. Wilkinson gives data for a very large kindred [*9*]. However, the matings necessary to test the hypothesis of incomplete dominance were not present, for there was only one mating of a person with xanthoma and only one mating of two hypercholesterolemic persons. The results of his study could be explained by the hypothesis of incomplete dominance but are equally well explained by the hypothesis of simple dominance. Thus the results of the foregoing studies are not in disagreement with the present study.

However, the possibility that the homozygous state produces a more severe form of the disorder has not been ruled out, and there are some data suggesting that children in whom xanthoma tuberosa and tendinosa develop at a young age with severe lipid abnormalities may represent this state.

The prevalence of familial hypercholesterolemic xanthomatosis is not known. It has been suggested by Adlersberg [*14*] and his associates [*15*] that familial hypercholesterolemia without xanthomatosis is the same disorder. Their studies demonstrated a prevalence of 4.1 to 5.5 per cent of familial hypercholesterolemia in hospital populations. However, tendon nodules were rarely observed in these persons and the prevalence of hypercholesterolemia in the children and siblings of affected persons was only about 35 per cent. These differences from the present study and from that of Piper and Orrlid suggest that the disorder or disorders studied by Adlersberg and associates were not the same as familial hypercholesterolemic xanthomatosis. Until the identity of these groups is established, the genetic and clinical data concerning familial hypercholesterolemic xanthomatosis cannot be applied with assurance to cases of idiopathic hypercholesterolemia.

CONCLUSIONS

1. Several diseases which appear to be, in part at least, genetically determined predispose persons to the development of atherosclerosis. These include diabetes, hypertension, idiopathic hyperlipemia and familial hypercholesterolemic xanthomatosis. Except for the last, the methods of inheritance of these disorders has not been settled.

2. Familial hypercholesterolemic xanthomatosis is associated with a high prevalence of coronary heart disease presumably as a result of a basic abnormality in lipid metabolism. It is inherited by simple Mendelian dominance. Hypercholesterolemia is present from early life, while the appearance of xanthoma and coronary heart disease is dependent upon time and the severity of the lipid abnormalities.

Acknowledgments: The author wishes to express his appreciation to the following physicians whose cooperation made the index cases and many members of their families available for study: John Cass, Charles Houston, Louis Kunian, Walter Lever, Farahe Maloof and Casimir Wozmak.

The author is greatly indebted to Mrs Dorothy Mannix for the long hours she spent assisting with the examination of these persons, and for her help with tabulation and analysis of the data. Mrs. Elvira Day and Mrs. Eleanor Searle assisted with the examinations of many of these patients during the early phase of this study.

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Clinico-pathologic Conference

Chronic Cough, Dyspnea and Cor Pulmonale

STENOGRAPHIC reports edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students. In the present conference an unusual departure from protocol was occasioned by the visit of Dr. Harry Zimmerman, Director of Laboratories at the Montefiore Hospital and Professor of Pathology at Columbia University in New York City. We should like to express our appreciation to him for conducting and editing the pathologic portion of this conference.

THE patient (No. 12,262) was a Negro man, forty-seven years of age, who was admitted to the Montefiore Hospital because of chronic cough and dyspnea of one year's duration. About one year before admission, he had a pain in the chest, cough and rusty sputum, associated with fever, which required hospitalization at another institution. A diagnosis was made of lobar pneumonia, and the symptoms subsided with penicillin therapy. During the ensuing year several episodes of exertional dyspnea and anterior chest pain occurred.

The patient had worked as a rock driller in a quarry from age twenty-seven to thirty-two. He was never edematous but usually slept on two pillows. Cough was chronic and productive of small amounts of yellow sputum.

Physical examination revealed the patient to be a very muscular adult in no acute distress. The anteroposterior diameter of the chest was increased; the lungs were clear. The heart was enlarged to the left with the point of maximal impulse in the sixth intercostal space at the anterior axillary line. A moderately harsh systolic apical murmur, somewhat distant heart sounds and a questionable gallop were heard. P2 was greater than A2. The liver and spleen were not felt. There was no clubbing of the fingers and no obvious cyanosis. The blood pressure was 120/80 mm. Hg and the pulse 88 per minute.

The laboratory data were as follows: Hemoglobin, 13.5 gm.; white blood cell count, 4,900/cu. mm. with a normal differential count. Urinalysis was negative. Blood serologic test for syphilis (Kolmer) was 4 plus. Spinal fluid serology was negative. Sputum was positive for Friedländer's bacilli, type A. Repeated cultures of sputums for acid fast organisms were negative. Blood urea nitrogen was 13 mg./100 ml. and the fasting blood sugar was 84 mg./100 ml. Serum electrolytes were normal.

A suspicion of pneumoconiosis was entertained and cor pulmonale with congestive heart failure was diagnosed. Congenital heart disease was also considered. Therapy consisted of aerosol penicillin, 0.1 gm. digitalis leaf a day for three weeks and frequent mercurials. Despite repeated recovery of Friedlander's organisms in the sputum, the patient remained afebrile. Blood serologic test for syphilis was positive on several repeated examinations. Following 8 million units of penicillin in fourteen days, a definite progressive fall in the serologic titer was noted.

The chief complaint remained marked shortness of breath on exertion. Roentgenograms of the chest revealed a fine reticular pattern in the upper halves of the lungs. Second strength old tuberculin gave a positive skin test. Electrocardiograms revealed right axis deviation. Fluoroscopic examination disclosed enlargement of the main branches of the pulmonary artery as well as increased size of the right ventricular inflow and outflow tracts; the aorta, the barium-filled esophagus and the left ventricle were normal.

The patient was subject to attacks of severe anxiety, marked hyperpnea and tachycardia after slight exertion. During the time of greatest stress he was able to lie flat and the electrocardiogram showed a rapid heart rate with very slight S-T depression. During the early part of the course in the hospital, while on digitalis, the patient's venous pressure and circulation time

were repeatedly normal, even during the attacks of dyspnea. Later in his course, while still taking a salt-poor diet and some considerable time after digitalis had been stopped, his venous pressure and the circulation time were abnormal (VP 14 cm. H_2O, rising to 16.5 on hepatic pressure; decholin® time, thirty-five seconds; ether time, thirteen seconds). The liver became palpable and tender, although the lungs remained clear. The patient responded quite well to administration of mercurials and diuretics, especially when ammonium chloride was also given. Oxygen saturation studies showed 19.7 volumes per cent in the femoral artery (97 per cent saturated), 9.6 volumes per cent in the vein. There was no change in saturation after exercise. Cardiac catheterization studies disclosed a low cardiac output; increased right auricular, right ventricular and pulmonary artery pressures (impression was that of a markedly increased pulmonary arterial resistance). Angiocardiography suggested impaired pulmonary blood flow. Angiography of the pulmonary vascular tree indicated enlargement of the entire right side of the heart and of the main pulmonary artery branches.

The patient was given a course of terramycin therapy and responded with diminution in cough and with an increased ability to exercise without dyspnea. During the five succeeding months of the patient's hospital residence, the blood urea nitrogen slowly rose to 55.8 mg./100 ml. He died unexpectedly during the night, about six months after his admission to the hospital.

CLINICAL DISCUSSION

Dr. Edward Reinhard: This forty-seven year old Negro gave a history of pain in the chest, cough, rusty sputum and fever, one year before his admission to the Montefiore Hospital. A diagnosis of pneumonia was made. He was treated with antibiotics and appeared to respond. However, thereafter he complained of persistent cough and dyspnea. He also suffered several attacks of anterior chest pain with exacerbation of the dyspnea. He had no acute symptoms. One can assume that he was admitted to the hospital for diagnostic studies because his condition was becoming progressively worse. In the past history, the most pertinent feature was the fact that this man worked as a rock driller in a quarry from about the age of twenty-seven to the age of thirty-two. Since he died at age forty-seven he had had no exposure to rock dust for a period of fourteen or fifteen years.

The diagnostic problem concerns the etiology of his chronic cough, dyspnea and cardiac disease. Dr. Humphreys, would you review the roentgenograms?

Dr. William Humphreys: The heart was enlarged in the frontal and in the oblique projections indicating that the enlargement was right ventricular and right auricular. No obvious left auricular enlargement was seen but there appeared to be some degree of left ventricular enlargement. The main and the hilar vessels were abnormally large. There were some sclerotic plaques in the aorta rather unusual in degree for a patient of this age. Pleural thickening was present bilaterally. In the lung fields an abnormal reticular pattern was seen which in general followed the distribution of the smaller pulmonary vessels. There was some linearity and nodularity in the densities, at the level of and immediately adjacent to these smaller pulmonary radicals. Examinations of the hands and feet were obtained in search for the lesions of sarcoidosis. No bony lesions were seen. A film obtained about four months after the first examination showed progressive enlargement of the right side of the heart. The parenchymal pulmonary markings appeared a little more linear indicating that the densities had been organizing. My diagnoses would be: pulmonary hemosiderosis; pulmonary arteriolar disease; pulmonary arteriolar hypertension; cor pulmonale; dilatation of the main and hilar pulmonary arteries; right ventricular, right auricular and left ventricular enlargement; arteriosclerosis in the aorta and dorsalis pedis vessels.

Dr. Reinhard: Do you think there were nodules in the lungs?

Dr. Humphreys: Yes. That was the basis for my first diagnosis, namely pulmonary hemosiderosis. The changes resemble those seen in chronic mitral stenosis.

Dr. Reinhard: Let us first consider the nature of this patient's cardiac lesion. We will then discuss the underlying pulmonary diseases which were possibly responsible for the cardiac lesion. The patient had a harsh but softened systolic murmur at the apex, a questionable gallop, and the second pulmonic sound was accentuated over the second aortic sound. Roentgenograms showed enlargement predominantly of the right side of the heart. The electrocardiogram taken shortly after admission showed only right axis deviation. The oxygen saturation of the femoral arterial blood was normal, and this was not

altered by exercise. I assume from these data that we may exclude the cyanotic forms of congenital heart disease as well as lesions producing an A-V shunt in the lungs. Dr. Bercu, will you begin the discussion.

Dr. Bernard Bercu: Any significant left to right shunt was ruled out at catheterization. In the absence of evidence of the usual types of heart disease associated with left ventricular hypertrophy and failure and with the major changes in the right side of the heart, one could reasonably exclude the possibility that left ventricular failure produced the pulmonary hypertension. We have no evidence to suggest mitral disease. On the basis of the catheterization data, pulmonary hypertension is probably the primary entity and the heart disease is secondary.

Dr. Reinhard: Dr. Smith, would you agree that this patient had cor pulmonale or do you think we must consider any other heart disease?

Dr. John R. Smith: The data are more compatible with cor pulmonale than with any other cardiac disease. The dyspnea suggests that there was significant occlusion of the pulmonary arteries. I visualize small pulmonary emboli as part of this process; it is not unlikely that these emboli may have incited pulmonary atherosclerosis. One other entity should be suggested. The patient's serology was positive and there were calcific plaques in the aorta. These data raise the question of syphilitic aortitis. While this diagnosis cannot be made here, it should be mentioned.

Dr. Reinhard: Would you comment on the fact that this patient, even during attacks of marked hyperpnea and tachycardia, was comfortable lying perfectly flat.

Dr. Smith: This phenomenon is frequently striking in persons who have obstructive pulmonary disease due either to pneumoconiosis or to emboli. The assumption is that the cardiac output may be increased by the horizontal position which enhances blood flow to the heart through the inferior vena cava.

Dr. Reinhard: The venous pressure and circulation time, when first measured, were normal, but during the later months of the patient's stay in the hospital, both values became significantly elevated. The liver became palpable although edema was never described. The patient was certainly in heart failure, and I shall assume in the remaining discussion that he had cor pulmonale secondary to pulmonary hypertension.

Dr. Goldman, this patient was a rock driller. Do we have to consider pneumoconiosis?

Dr. Alfred Goldman: The history is lacking in important details. We should like to know exactly what his occupation was; what he used in drilling rock; whether or not he used a jack hammer; whether or not water was used in the process; whether or not he wore a mask; whether he was on the inside or the outside? The kind of rock of course would also be important. However, he worked at this occupation for only four years—not a long industrial history for the production of pneumoconiosis. Further, the symptoms started fifteen years later. If the symptoms were related to drilling he probably would have had trouble long before. The x-ray is compatible with silicosis but the process certainly was not very extensive. Often one cannot predict from the roentgenogram the degree of dyspnea or disability that a person may have, particularly when the silicosis affects the blood vessels and does not produce large shadows. In this case, silicosis can be discounted as a possible cause of the pulmonary hypertension.

Dr. Reinhard: Dr. Harford, will you discuss the presence of Friedländer's bacilli repeatedly found in the patient's sputum? The organism is certainly a pathogenic one but can occasionally be cultured from the sputum, and rarely from the stool, of normal individuals.

Dr. Carl Harford: In the field of classification of bacteria, this particular group produces a tremendous amount of confusion. People use the terms Friedländer, Klebsiella and Aerobacter. I assume that in this case, the organism was a coliform bacillus with a mucoid colony and a capsule and that a specific swelling reaction was obtained with the type A antiserum. Under these circumstances it is usually stated that in about 5 per cent of cultures from the respiratory tract the organism may be obtained. Although we do not routinely type the Friedländer organism in our laboratory, we find mucoid encapsulated coliform bacilli more frequently than that.

Dr. Reinhard: This patient remained completely afebrile throughout his hospital course. His white blood cell count on admission was 4,900 per cu. mm. with a normal differential leukocyte pattern. Do you think we are safe in assuming that he did not have a significant Friedländer's bacillus infection of the respiratory tract?

Dr. Harford: I think we are safe in saying

that he did not have acute Friedlander's pneumonia which is usually a very severe type of pneumonia with a high case fatality rate. Cases of chronic infection of the lung with Friedländer's bacillus have been described which sometimes simulate pulmonary tuberculosis or bronchiectasis. Most of these patients have fever, or some change in the white blood count or differential. However, there are rare patients who have normal leukocyte levels. In this case it is unlikely that the Friedländer's bacillus was concerned in a pulmonary infection.

Dr. Reinhard: Our "host" was apparently living in peaceful symbiosis with these bacteria. We seem to be in agreement that the patient had cor pulmonale due to pulmonary arterial hypertension from increased vascular resistance in the lungs. The next question concerns the type of pulmonary lesion which can produce these events. Mitral valvular disease has already been mentioned but seems unlikely. Emphysema may produce these changes, and the patient did have some degree of emphysema, but it seems improbable that this condition could explain the entire clinical course. Widespread tuberculosis, extensive disease of the lungs with pneumonectomy and severe kyphoscoliosis can also invoke cor pulmonale. There is certainly nothing in our patient's story to suggest any of these diseases. Diffuse pulmonary arteriosclerosis must be seriously considered.

Dr. Bercu: In the absence of arterial-venous shunts and in a person with pulmonary hypertension the diagnosis of diffuse pulmonary arteriosclerosis must be entertained and is difficult to rule out. However, in my experience the lung fields are fairly clear in this disorder.

Dr. Sol Sherry: Primary pulmonary arteriolar hypertension would have to be considered. I would be interested in knowing what the pulmonary wedge pressure was, because usually the pulmonary capillary pressure is normal in the face of pulmonary arteriolar constriction.

Dr. Bercu: I would assume that the wedge pressure was probably normal. If the wedge pressure is accurately measured (by that I mean the catheter is wedged into a peripheral arteriole), one is actually measuring capillary pressure. Real wedge pressure should approach left auricular pressure.

Dr. Reinhard: For example, if we had a lesion obstructing the arteries in the lung, then wedge pressure would be normal, perhaps even low, since the blood that gets into the capillaries is eliminated.

Dr. Bercu: Correct.

Dr. Reinhard: It seems important to note that all the lesions mentioned thus far would not be likely to cause nodularity of the lung. I have been inclined to eliminate all of them on that basis. Multiple pulmonary emboli does however suggest itself as the next diagnosis to be considered. Dr. Smith, what is the possibility that this patient might have had multiple emboli to the lung that were so small that none of them produced an infiltrate of any size and yet accounted for these tiny nodules?

Dr. Smith: Experimentally one can inject miliary suspensions of fibrin, for instance, into the venous blood stream to embolize the lung and ultimately to produce pulmonary atherosclerosis in rabbits and dogs. If showers of emboli occurred slowly, cor pulmonale should result. As a matter of fact, this event seems to have occurred in a number of cases described by Owen et al.* Nobody knows where these miliary emboli originate but they apparently are so small when they reach the lungs that they impact the vessels which are near arteriolar size. The literature reports that there may be resultant pulmonary shadows of one type or another, although they are not very clearly described.

Primary pulmonary thrombosis involving moderately large pulmonary vessels may be so extensive as to imitate pulmonary embolism with resultant cor pulmonale. It is rare and the process should have been more acute than it was in this patient. In many of the cases of so-called primary pulmonary thrombosis, there is no distinct underlying lesion and the cause of the thrombi has remained uncertain.

Dr. Reinhard: Other possible diagnoses may be considered under the heading of chronic fibrotic pulmonary disease, such as diffuse interstitial fibrosis. There are perhaps several varieties of this process, one of which is the Hamman-Rich syndrome.

Dr. Bercu: All the data in our patient are compatible with this possibility.

Dr. Humphreys: Dr. Reinhard, I believe there is more cardiac involvement than there is pulmonary disease which would be just the

* Owen, W. R., Thomas, W. A., Castleman, B. and Bland, E. F. Unrecognized emboli to the lungs with subsequent cor pulmonale. *New England J. Med.*, 249: 919, 1953.

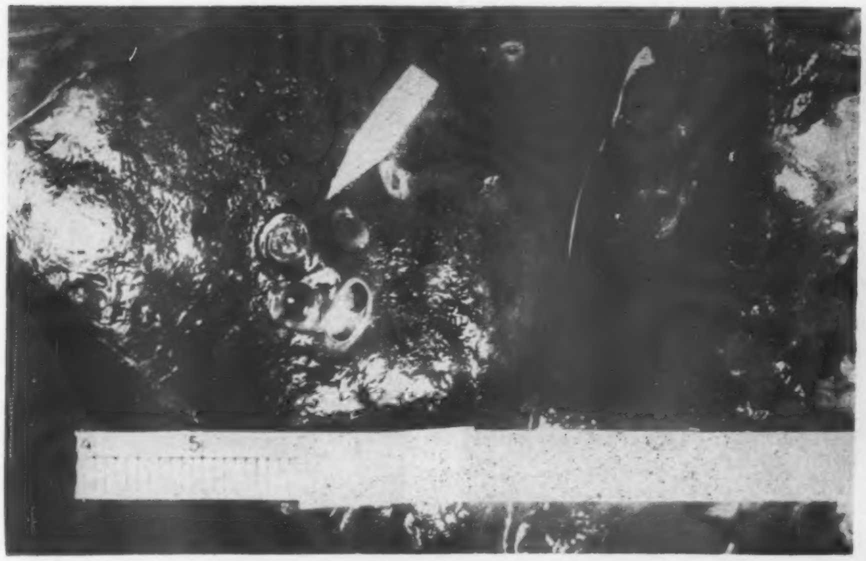

FIG. 1. Occlusion of pulmonary artery by organizing embolus.

reverse of what is seen in the Hamman-Rich syndrome.

DR. REINHARD: Scleroderma can sometimes produce a fibrotic reaction in the lung. I am inclined to dismiss this possibility because there is nothing to go along with the diagnosis. Sarcoidosis is a lesion which is sometimes associated with considerable pulmonary fibrosis and nodulation. Berylliosis is also a possibility. Dr. Moore, will you discuss these?

DR. CARL MOORE: There are no supporting data for either diagnosis and the prominence of the cardiac manifestations makes both unlikely.

DR. SHERRY: If we are dealing with a primary pulmonary disease involving pulmonary tissue we would expect an alveolar capillary-block and cyanosis would be a prominent feature, especially with effort. In view of this, I believe we must place the lesion in the pulmonary vascular tree.

DR. REINHARD: The final diagnoses suggested are these: Cor pulmonale due to pulmonary hypertension; pulmonary vascular obstruction, probably embolic or thrombotic in origin, severe cardiac failure, predominantly right ventricular; treated syphilis which was unrelated to the terminal illness. Granulomatous or fibrotic disease of the lungs cannot be excluded although these would be more apt to produce alveolar-capillary block with cyanosis.

PATHOLOGIC DISCUSSION

DR. HARRY ZIMMERMAN: I have not deliberately withheld any information. No wedge pressures were taken. The man did work out of doors in a quarry, but I do not know the kind of granite he was working on. For this he used a jack hammer. He did not wear a mask nor was he injected with any glass beads. This man was a very muscular person, weighing 74 kg. He did not have any anatomic syphilis and he did not have Ayerza's disease, which was considered at our hospital although he had never been out of the country. He was born in New York and remained there all his life.

The lungs bilaterally were peppered in their smaller arterial branches with numerous antemortem blood clots. (Fig. 1.) This points to an atheroma in a vessel which was distally occluded by an organized embolus. Many vessels of the lungs showed this picture. The emboli were in various stages of organization. Many of the terminal arterioles in both lungs were involved in this fashion, and extending in a retrograde manner, that is, back toward the heart, there were superimposed organizing thrombi. None of the major pulmonary arteries was occluded. There was minimal pulmonary fibrosis.

We found none of the characteristic lesions of berylliosis and the patient did not break fluorescent lights. He had worked after his quarry experience for a period of some years as a binder in a paper factory, and then had done some janitorial work in a housing project. As far as we know, the lesions of siderosis were not present in this subject. He had no siderotic nodules in either lung to account for the picture one saw by x-ray. It was my belief, and I hope you will agree with

Fig. 2. Inflow tract of the hypertrophied and dilated right ventricle. Note also the greatly enlarged right atrium.

Fig. 3. Outflow tract of the right ventricle, disclosing the greatly enlarged conus pulmonalis.

me, Dr. Humphreys, that the little nodularities noted in the roentgenograms were occluded arterioles seen on cross section. At any rate, there were no fibrotic lesions and no evidence of siderosis. Nor were there evidences of infarcts in these lungs. The fact that all stages of organization of blood clots were present, makes us believe that these insults to the lung were on the basis of multiple vascular embolizations which occurred over a period of considerable time.

There was evidence of pulmonary hypertension determined on the basis of atherosclerosis of some of the pulmonary arterial radicles. There was much less atherosclerosis of the aorta than of the pulmonary arteries. There was no evidence of syphilitic involvement.

The right lung weighed 900 gm. which is considerably heavier than normal, and the left weighed 800 gm. The heart weighed 550 gm., and even though the patient was a muscular person, there was considerable cardiac hypertrophy and some cardiac dilatation. The heart was almost round with the apex of the right ventricle extending to the very apex of the heart itself, indicating a predominantly right sided hypertrophy. (Figs. 2 and 3.) There was an enormous tricuspid valve which was not involved by any inflammatory process. The right ventricle was huge with marked hypertrophy of the papillary muscles. The outflow tract of the right ventricle was quite large. There was a large cor pulmonale with no involvement of the pulmonic cusps themselves. There was relatively little involvement of the left auricle either by dilatation or hypertrophy. The mitral valve was entirely normal and there was a dilatation of the left ventricle, but only of a minimal degree.

And now for the source of the pulmonary emboli. It has been mentioned that such a source is not always found and that is quite true, but in this case we were somewhat more fortunate. In dissecting out the prostatic plexus, many of the blood vessels were found thrombosed and the thrombi were in various stages of organization. Some had been organized *in situ;* others were still quite fresh. Rather careful examination was made of the veins of the legs, the iliacs, the femorals and the popliteals; they were all normal. Microscopic studies of the lesions in the lung failed to reveal inflammatory vascular changes, but there were thrombophlebitic changes in the prostatic plexus.

The kidneys were essentially normal without evidence either of pyelitis or of arteriolar vascular disease. The liver showed severe chronic passive congestion with early cardiac cirrhosis. It weighed only 1,800 gm., which is slightly heavier than average. The spleen weighed 400 gm., which is considerably enlarged. It was firm and also the seat of chronic passive congestion.

The lungs were analyzed for silica and it was found that there was only a trace of silicon dioxide per gram of dried lung tissue. For this reason it was concluded that not only was there no anatomic silicosis but that there was no chemical

silicosis as well. There was no evidence of pneumonitis and we agree that the presence of Friedlander bacilli in this case was in the nature of a red herring. I already mentioned the fact that there was no aortitis. He had no sarcoidosis anywhere, including the lungs. We did not find pulmonary siderosis either, and there was no mitral stenosis. Perhaps one should not even have suspected it. We found no evidence of aortic calcification, and it intrigues me that roentgenologically such a suggestion was made. I have seen such diagnoses made frequently without being able to confirm them always anatomically.

Case Reports

Megaloblastic Anemia Associated with Diverticula of the Small Bowel*

Stuart R. Townsend, m.d. *and* Douglas G. Cameron, m.d.
Montreal, Quebec

During the past two years we have had the opportunity to study three patients with moderate megaloblastic anemia and diverticula of the duodenum and small bowel. Early in 1954 such an association of findings had not been reported and we speculated on the possible relationship between the anemia and the diverticula. It is known that a megaloblastic anemia follows total gastrectomy and occasionally occurs after partial gastrectomy [*1*] or strictures and anastomoses [*2*] of the small bowel. Macrocytic anemia has been reported in association with artificial diverticula of the small intestine in experiments performed on rats [*3*] and it seemed reasonable that a similar association might exist in naturally occurring diverticula of the small bowel in man. A case report by Dick [*4*] appeared to justify this hypothesis and continuation of our studies in such cases.

This report deals with the findings in three patients and a discussion of the possible role of small intestinal diverticula in the pathogenesis of megaloblastic anemia.

Our three patients were women with megaloblastic anemia in whom diverticula were demonstrated in the duodenum, jejunum and ileum. None had undergone gastrointestinal surgery. Their ages ranged from fifty-nine to eighty years. Two had lost weight. One patient had free hydrochloric acid in the gastric juice but did not have steatorrhea. These findings seemed to exclude a fortuitous association of small intestinal diverticulosis with pernicious anemia or idiopathic steatorrhea in this case. One of the remaining patients had gastric achlorhydria and latent steatorrhea, while the other had gastric achlorhydria but did not have steatorrhea. In two patients it was possible to demonstrate stasis in the diverticula for a period of hours. One patient had a mild prothrombin deficiency. There was no evidence of iron deficiency, renal or liver disease in any of these cases. Osteomalacia or clubbing of the fingers was not demonstrated.

Fat balance studies were undertaken in each case. The daily diet was calculated from food tables to contain 70 gm. of fat, 60 gm. of protein and 360 gm. of carbohydrate; 70 gm. of fat were contributed by three foods—milk, butter and eggs. Observations were made over an eight-day period in two patients and six days in one. One patient (Case i) had evidence of a latent steatorrhea. Faecal nitrogen values in this patient excluded a pancreatic origin for the condition.

Treatment in all cases was instituted with parenteral vitamin B_{12} alone. In two patients (Cases i and iii) the reticulocyte response was irregular but in spite of this normal red cell count and hemoglobin values were reached and maintained with this therapy alone. General improvement in health, with gain in weight and clearing of the glossitis (Case i), occurred in both patients. In one patient (Case ii) B_{12} therapy resulted in a retikulocyte peak, although not quite as high as would be anticipated in pernicious anemia. However, we are of the opinion that this diagnosis cannot be excluded in this patient. General improvement in health also resulted, with gain in weight and clearing of the glossitis. No other form of treatment was required to complete the control of the megaloblastic anemia in any of the three patients. A general sense of well-being, with normal blood values, has been maintained with parenteral vitamin B_{12} therapy for almost two years in all three patients.

* From the McGill University Clinic of The Montreal General Hospital. Presented in part at the vi Congress, International Society of Hematology, Boston, Massachusetts, August 27, 1956.

CASE REPORTS

CASE I. A seventy-nine year old woman had suffered weakness and fatigue for a year. She presented with weight loss, glossitis and megaloblastic anemia (red cell count, 2.23 million per cu. mm.; packed red cell volume, 21 per cent and hemoglobin, 6.8 gm. per cent). A sternal puncture showed megaloblastic bone marrow. Her tongue was smooth and atropic. There was no free hydrochloric acid in the gastric juice and no neurologic abnormality. The serum iron (75 μg.) and unsaturated iron binding capacity (300 μg.) were within normal limits. The serum vitamin B_{12} (266 $\mu\mu$g.) was low. Fat balance studies over an eight-day period revealed latent steatorrhea (daily fecal fat 13 gm., representing 18 per cent of intake; daily fecal nitrogen, 1.5 gm.)

CASE II. An eighty year old woman presented with a history of weight loss, paresthesia of the hands and feet, and megaloblastic anemia (red cell count, 2.96 million per cu. mm.; packed red cell volume, 26 per cent and hemoglobin, 10.1 gm.). Sternal puncture revealed megaloblastic bone marrow. Her tongue was not smooth or atrophic. There was no free hydrochloric acid in the gastric juice and no neurologic abnormality was demonstrated. The serum iron (63 μg.) and unsaturated iron binding capacity (240 μg.) were within normal limits. There was no steatorrhea (daily fecal fat, 4.6 gm. and daily fecal nitrogen, 0.64 gm.). The serum vitamin B_{12} (188 $\mu\mu$g.) was low.

CASE III. A fifty-nine year old woman was admitted with abdominal discomfort and anorexia. Investigation revealed no weight loss but she had a megaloblastic anemia (red cell count, 2.4 million per cu. mm.; packed red cell volume, 20 per cent and hemoglobin, 7.2 gm.). Sternal puncture showed a megaloblastic bone marrow. The prothrombin time (twenty-three seconds) was prolonged. Free hydrochloric acid was present in her gastric juice. There was no glossitis and no neurologic disorder. The serum vitamin B_{12} (203 $\mu\mu$g.) was low. The serum iron (55 μg.) and unsaturated iron binding capacity (368 μg.) were within normal limits. There was no steatorrhea (daily fecal fat, 5.5 gm., and fecal nitrogen, 0.66 gm.).

COMMENTS

Duodenal diverticula are not uncommon in most hospital populations. They are often associated with diverticula in the jejunum and ileum. Many are demonstrated in the course of barium investigations to elucidate vague gastrointestinal symptoms. Traumatic rupture, perforation, fistula, hemorrhage and obstruction have been reported [*5*]. The importance of hemorrhage from jejunal diverticula has been emphasized in a number of cases [*6*].

The syndrome of obstruction, consisting of vague abdominal discomfort, colic, nausea, vomiting and constipation, has been described and attributed to defective voluntary movement of the bowel [*7*]. In 1949 a case was reported in which there was a lowered serum protein, raised fecal fat and some diarrhea [*8*]. It is possible that a deficiency syndrome existed in this case, although this was not suggested by the author. A deficiency syndrome, consisting of small intestinal diverticula, steatorrhea and megaloblastic anemia, was clearly described in 1955 [*4*]. Similar reports in British literature have followed [*9,10*].

Manifestations of steatorrhea following operations on the gastrointestinal tract are protean. In our cases of diverticula of the small bowel the manifestations were equally variable. They included weight loss, glossitis, prothrombin deficiency, achlorhydria, latent steatorrhea and megaloblastic anemia. They may occur singly or in combination and occasionally, no doubt, all findings might occur in the same patient.

The abnormal mechanism in diverticula of the small bowel may operate in a manner similar to that which occurs in gastrocolic fistula or enterocolic anastomoses. Stagnation has been demonstrated in the diverticula and often exists for some time. With this stagnation a changing bacterial flora may be an important factor. These are the factors which seem to operate in the experimental bowel anastomoses in rats in which a macrocytic anemia developed.

SUMMARY

A study of three cases has shown that weight loss, glossitis, megaloblastic anemia, prothrombin deficiency, gastric achlorhydria and steatorrhea may occur in association with diverticula of the small bowel. Iron deficiency, osteomalacia and clubbing of the fingers have not been encountered to date.

The mechanism by which small bowel diverticula produces megaloblastic anemia is obscure. As in the malabsorption syndrome, elucidation of the mechanisms involved must await further knowledge. However, in our three cases the serum vitamin B_{12} levels were low and the hematologic responses to parenteral vitamin B_{12} therapy were satisfactory. This strongly suggests that megaloblastic anemia was due to a vitamin B_{12} deficiency.

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Gangrene of the Fingers in Periarteritis Nodosa*

G. AUSTIN GRESHAM, M.D. *and* DAVID N. PHEAR, M.D.
Cambridge, England

RAYNAUD'S phenomenon commonly occurs in disseminated lupus erythematosus but it is rarely seen in periarteritis nodosa [*3*]. Gangrene of the extremities is also rare in periarteritis nodosa. Several authors have described small necrotic plaques on the digits, but only two cases with massive digital gangrene have been reported [*1*,*2*].

We here describe a case of periarteritis nodosa with recent severe Raynaud's phenomenon, rapidly progressing to gangrene of all the fingers.

CASE REPORT

A man, aged thirty-one, was admitted to the hospital on August 12, 1954. During the three weeks before admission he had had attacks of pallor and coldness of the fingers, lasting for ten minutes at a time. For a week the fingers and thumbs had been persistently blue-grey and painful. On the day before admission the ankles became swollen and red. He did heavy work in a timber-yard and used no vibratory tools.

On admission, the terminal parts of all the fingers were dusky white, cold and extremely tender. Cutaneous sensation was impaired over the finger-tips. The toes were normal. There was erythema and oedema over the ankles, with a macular erythematous and purpuric rash over the lower shins and dorsal surfaces of the feet. Radial pulses and pulses in the feet were normal. The blood pressure was 175/115 mm. Hg.

The urine contained much protein with abundant red cells and a few granular casts. The leukocyte count was 14,000 per cu. mm. with 85 per cent polymorphonuclears, 6 per cent lymphocytes, 7 per cent monocytes and 2 per cent eosinophils. The erythrocyte sedimentation rate (Westergren) was 100 mm. per hour. No lupus erythematosus cells were seen. Blood urea was 33 mg. per cent and serum protein 8.8 gm. per 100 ml. with excess of α 2 and γ globulins. A radiograph of the chest was normal. An electrocardiogram showed left bundle branch block.

In spite of treatment with corticotrophin, priscol and nicotinic acid the fingers continued to deteriorate. Bilateral brachial plexus block and intra-arterial priscol produced flushing up to the ischaemic zone, but no improvement of the finger tips. Pain became increasingly severe and the finger tips became frankly gangrenous. (Figs. 1 and 2.) Amputation of all eight fingers through the middle or terminal phalanges was therefore performed on December 15, 1954 (Mr. R. W. Butler and Mr. T. J. Fairbank). Following amputation his general condition improved considerably and he was discharged on January 26, 1955 continuing treatment with corticotrophin gel, 30 mg. daily.

He was readmitted on February 28, 1955. During the past ten days both legs had become swollen up to the groins, with a purpuric rash. He was now dyspnoeic on slight exertion. The blood pressure was 180/100 mm. Hg. Both legs were conspicuously oedematous and there was tenderness over the right femoral vein in the mid-thigh. Râles were heard at both lung bases. A radiograph of the chest showed an area of consolidation in the right costophrenic angle suggestive of a pulmonary infarct. The blood urea was now 106 mg. per cent. Again no lupus erythematosus cells were found. A diagnosis of bilateral femoral vein thrombosis and pulmonary infarction was made. With rest and a low salt diet the oedema subsided. He was discharged on March 11, 1955 taking 25 mg. corticotrophin gel daily.

After discharge he became increasingly dyspnoeic and was readmitted on March 21, 1955. He was cyanosed and orthopnoeic. Coarse râles were heard throughout both lungs. Treatment was of no avail. He began to cough up profuse bloodstained sputum, and died with acute pulmonary oedema on the same day.

At necropsy the heart was enlarged mainly due to left ventricular hypertrophy. The right femoral vein was filled with old adherent thrombus and recent thrombus was lying loose in the iliac veins on both sides. There was moderate oedema of both lungs and each pleural sac contained approximately 300 ml. of clear yellow fluid. A brown triangular area of induration, 2 by 1 cm., was seen in the anterior basal segment of the right lower lobe. The kidneys were large and pale.

* From the Addenbrooke,s Hospital, Cambridge, England.

Fig. 1.

Fig. 2.

The cortex was pale and broad, studded with purple dots and with the normal striate pattern obscured.

Histologic examination of the amputated fingers showed necrosis of all parts of the digital tissue, together with infiltrations of polymorphonuclear leukocytes in the walls of small arteries.

In the kidneys small arteries showed lesions of periarteritis. Most glomeruli were enlarged with areas of focal fibrosis, capsular adhesions and epithelial crescents. The area of the lungs seen macroscopically was an infarct. Serial sections of the "conducting tissue" of the heart were examined. No lesion was found which could explain satisfactorily the left bundle branch block, although occasional small foci of polymorphonuclear leukocytes were seen in the ventricular septum.

Arteries in the stomach serosa, suprarenal and pectoral muscle also showed recent lesions of periarteritis.

SUMMARY

A case of periarteritis nodosa is described, presenting with severe Raynaud's phenomenon rapidly progressing to gangrene of all the fingers.

Acknowledgment: We are grateful to Dr. Laurence C. Martin for permission to publish this report.

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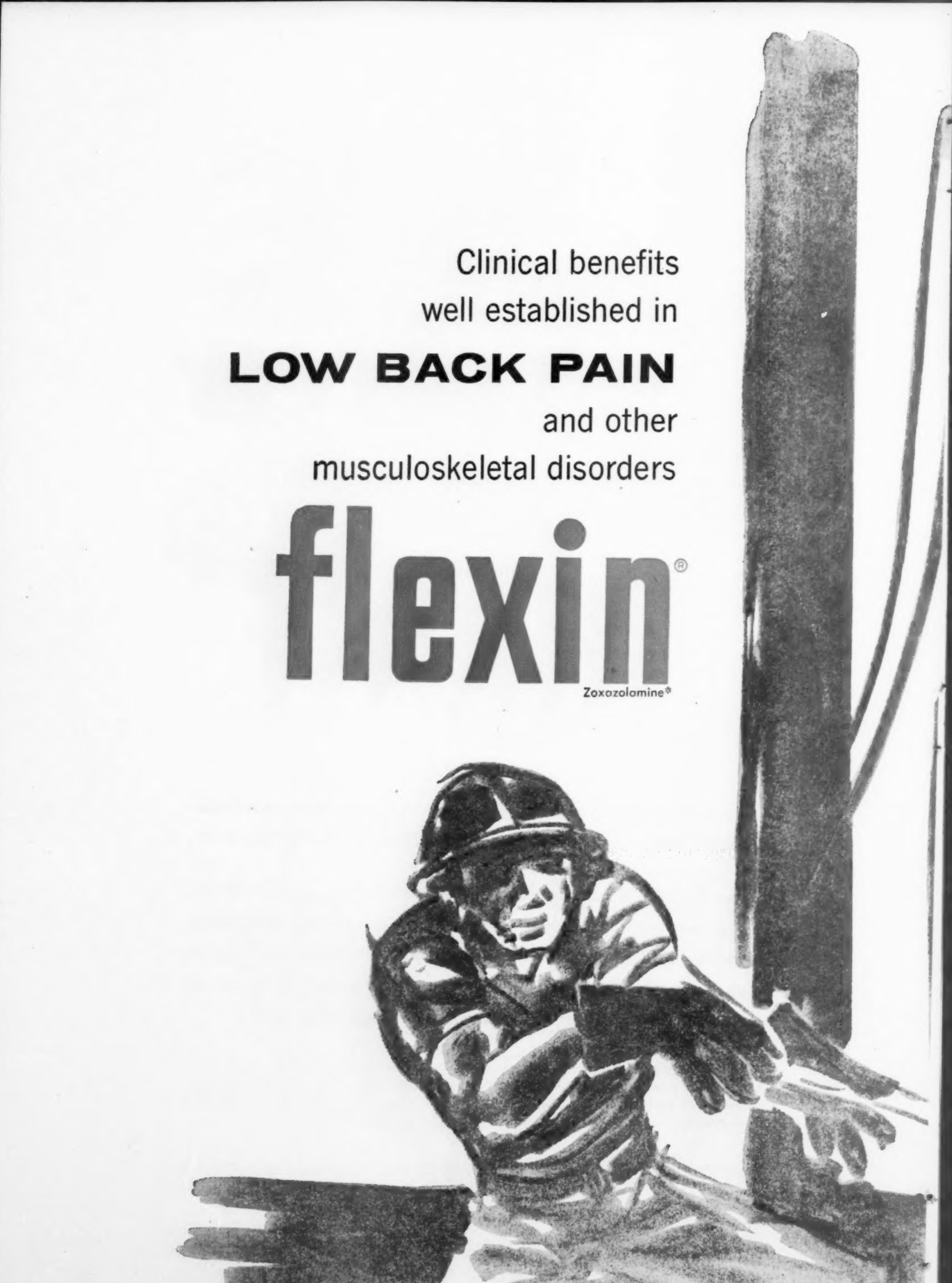

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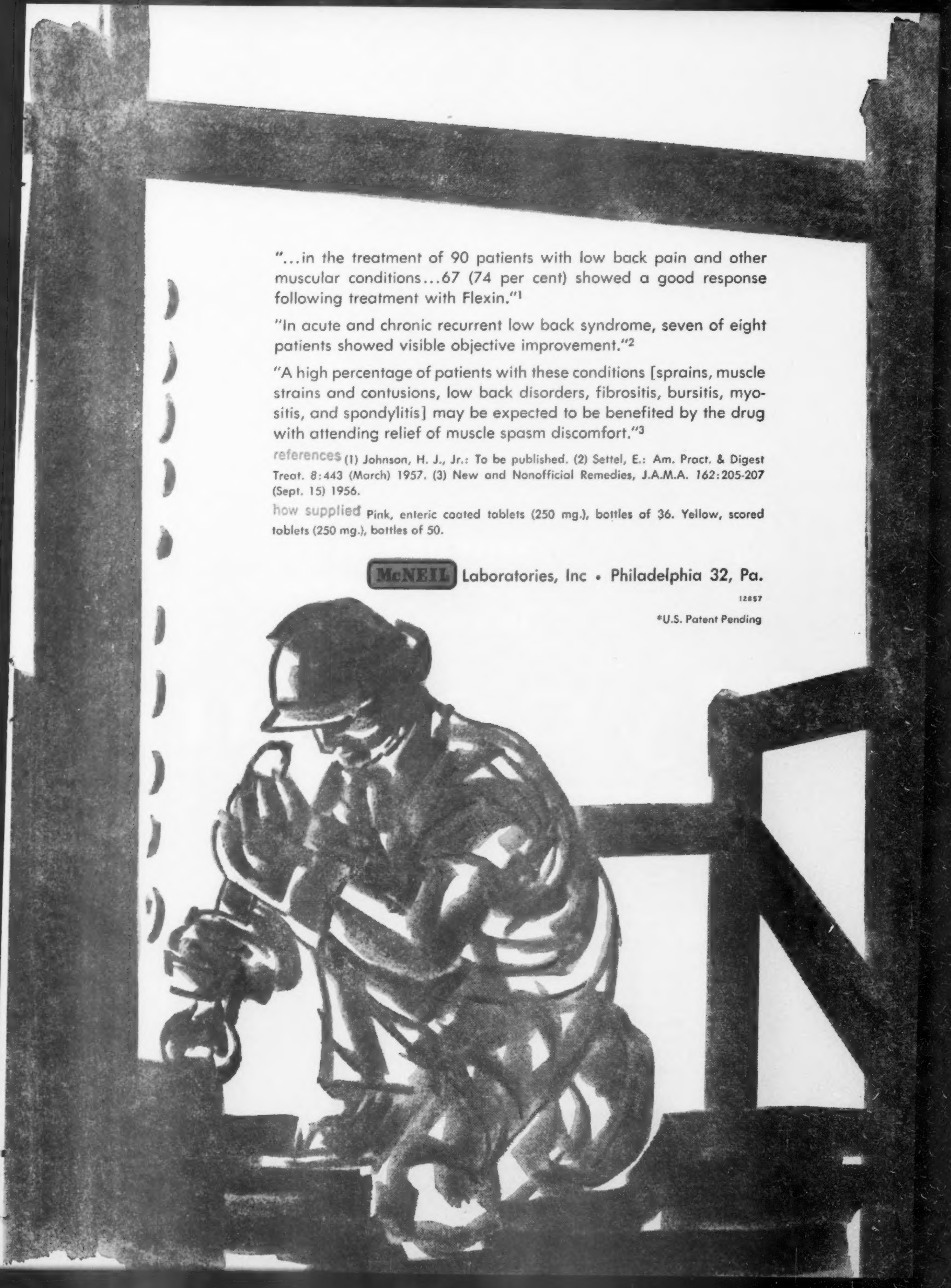
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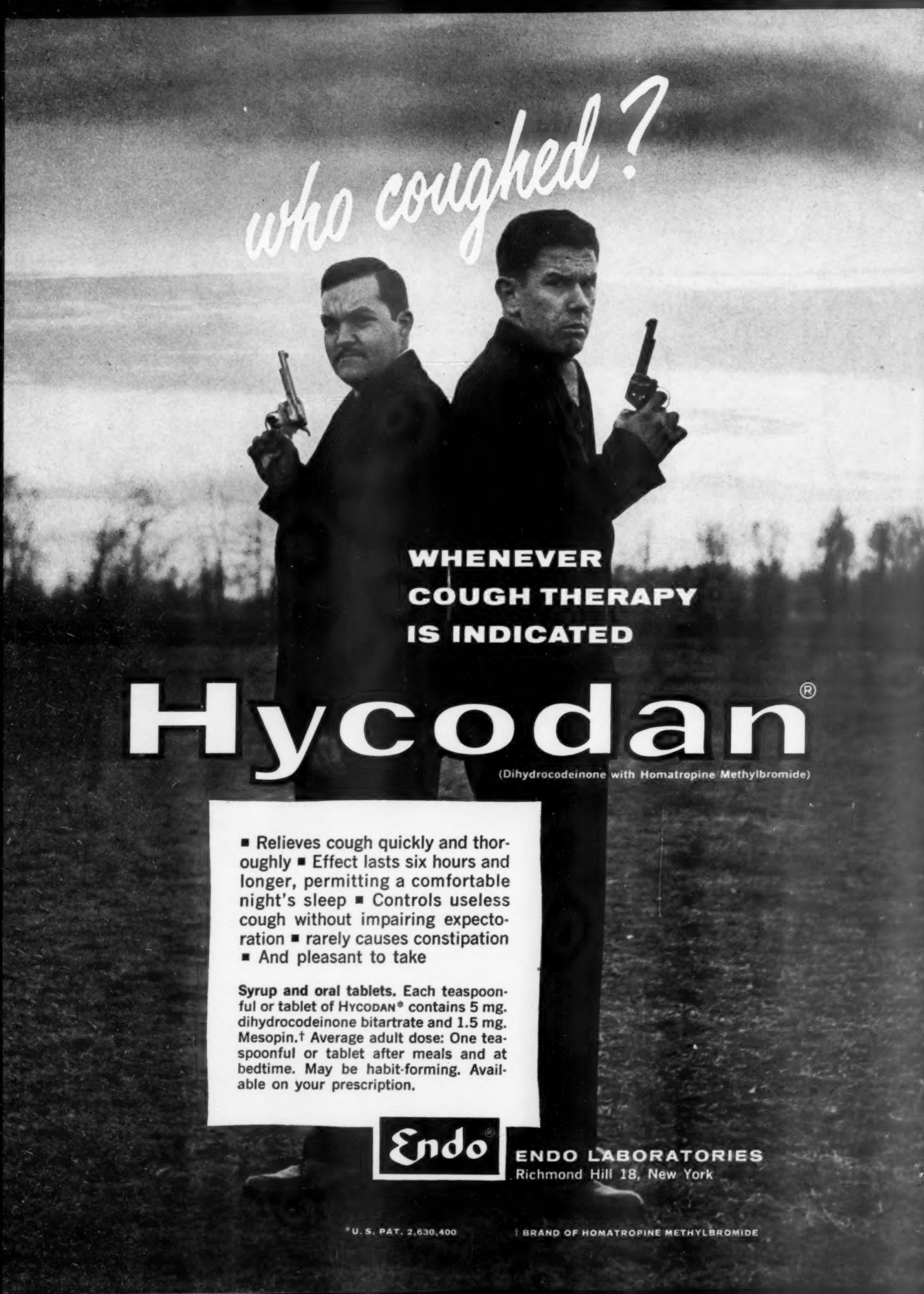
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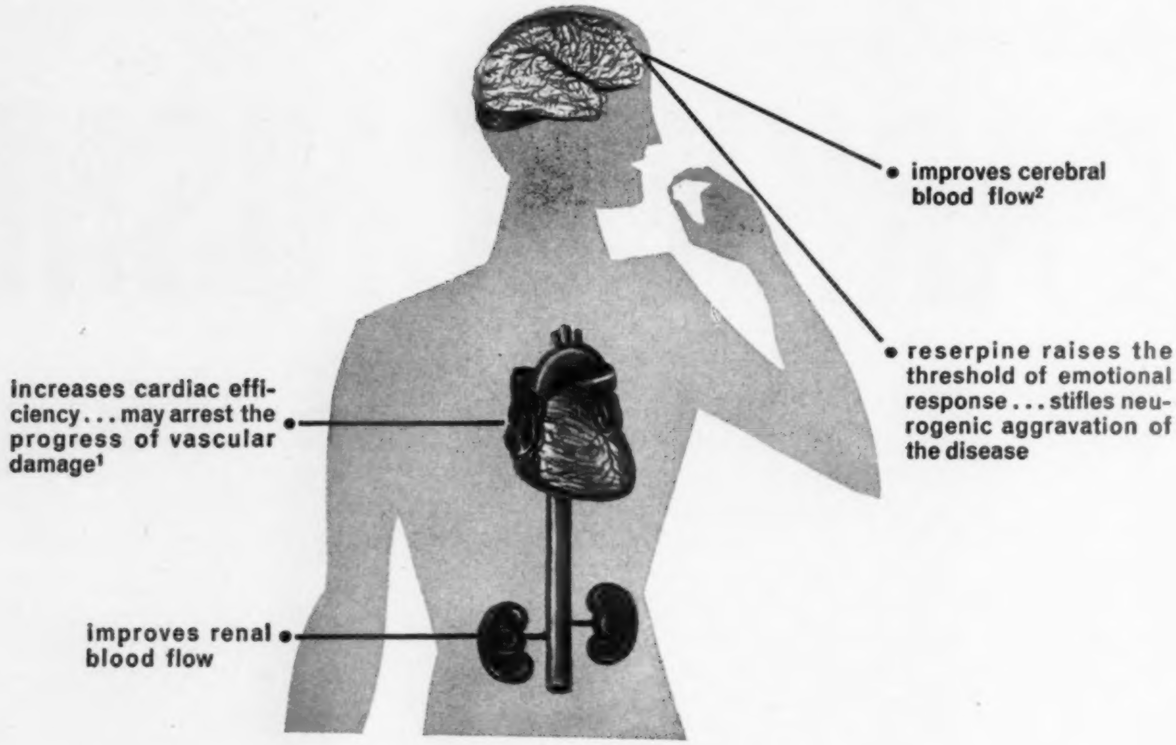

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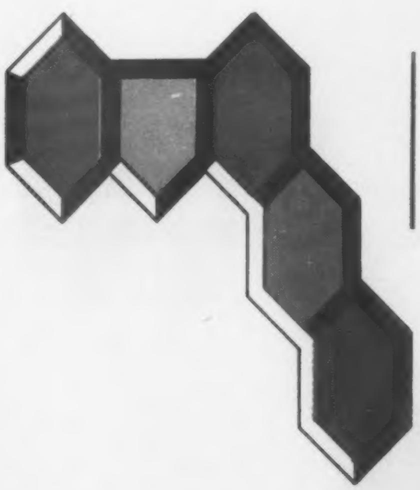

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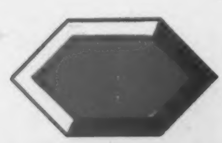

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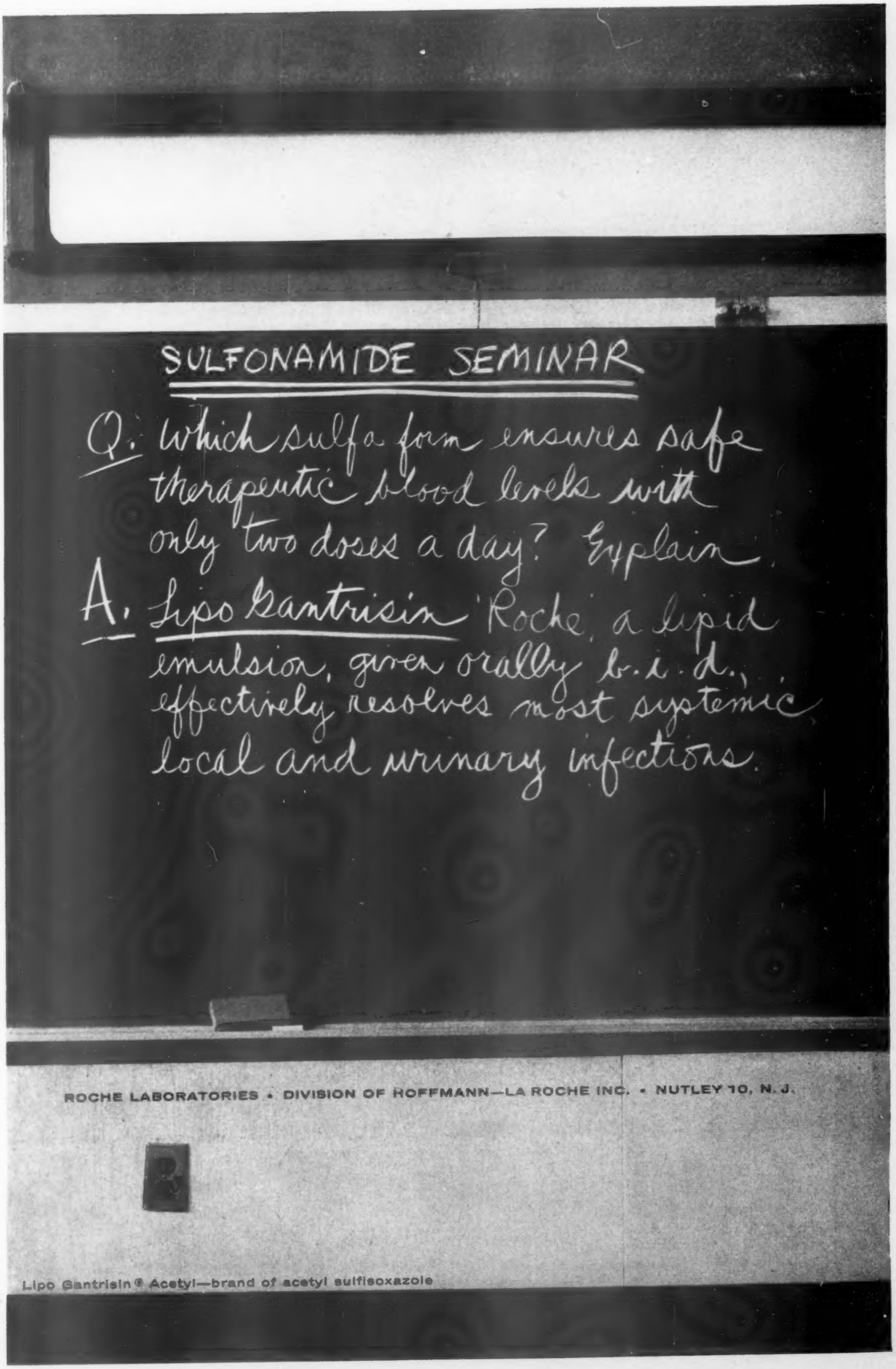
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